439

NCI/ICRDB/SL-439

PB81-929411

SPECIAL LISTING

# CURRENT CANCER RESEARCH

on

# PEDIATRIC NEOPLASMS

NEWARK PUBLIC LIBRARY
SEP 18 1981
U.S. GOVT. PUBN.
DEPOSITORY 378

**AUGUST, 1981**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service ● National Institutes of Health ●
National Cancer Institute

READEX FICHE best copy available

A SERVICE OF THE
INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

HE 20.3173:

**Dear Cancer Researcher**:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 55 areas are covered in separate **SPECIAL LISTINGS**. Each title of these **SPECIAL LISTINGS** is published annually.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 80 different countries.

Descriptions of more than 20,000 other current cancer-related projects are on the CANCERPROJ data base. This cancer data base is available as part of the MEDLINE System of the National Library of Medicine and can be searched by librarians at some 1400 locations in the U.S. and in 12 other countries. CANCERPROJ is also available via the new EURONET data base system in EUROPE.

Researchers who have summaries (project descriptions) in a given **LISTING** automatically receive complimentary copies of that **LISTING**. Additional copies of this **LISTING** or other **LISTINGS** can be purchased from the National Technical Information Service (see order form in back of this **LISTING**).

These **LISTINGS** are prepared for the ICRDB Program by the Current Cancer Research Project Analysis Center (CCRESPAC) which is operated by the Smithsonian Science Information Exchange (SSIE).

Investigators are urged to prepare accurate summaries of their research projects for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS**. The Project Registration Form found in the back of this **LISTING** should be used to register a new research project, update an out of date summary, and to notify the Program of changes in your address. Please send your correspondence to:

CCRESPAC Project Officer
ICRDB Program Office
National Cancer Institute
Westwood Building
Room 10A18
5333 Westbard Avenue
Bethesda, MD 20205

# RESEARCH AREAS

| | Abstract Number |
|---|---|
| **I. ETIOLOGICAL AND EPIDEMIOLOGICAL STUDIES OF PEDIATRIC NEOPLASMS** | 1 |
| A. FAMILIAL, GENETIC AND CONGENITAL FACTORS AND THE INCIDENCE OF CHILDHOOD CANCER | 1 |
| B. IN UTERO EXPOSURE TO EXOGENOUS ESTROGENS AND OTHER AGENTS AND THE INCIDENCE OF CHILDHOOD CANCER | 21 |
| C. IATROGENIC EXPOSURE TO RADIATION AND DRUGS AND THE INCIDENCE OF CHILDHOOD CANCER | 37 |
| D. DEMOGRAPHIC AND OTHER ETIOLOGIC FACTORS AND THE INCIDENCE OF SPECIFIC CHILDHOOD CANCERS | 58 |
| 1. LEUKEMIA AND LYMPHOMA | 58 |
| 2. NEPHROBLASTOMA AND OTHER SOLID TUMORS | 80 |
| E. OTHER ENVIRONMENTAL AND ETIOLOGIC FACTORS AND THE INCIDENCE OF CHILDHOOD CANCER | 91 |
| **II. PRECLINICAL CHEMOTHERAPY STUDIES IN MODEL SYSTEMS OF PEDIATRIC NEOPLASMS** | 114 |
| **III. CLINICAL DIAGNOSIS AND PROGNOSIS OF PEDIATRIC NEOPLASMS** | 122 |
| A. DIAGNOSIS OF CHILDHOOD CANCER | 122 |
| B. PROGNOSTIC FACTORS IN CHILDHOOD CANCER | 142 |
| **IV. CLINICAL THERAPY OF PEDIATRIC NEOPLASMS** | 159 |
| A. THERAPY OF LEUKEMIA, LYMPHOMA AND HISTIOCYTOSIS | 159 |
| B. THERAPY OF INTRACRANIAL TUMORS, NEUROBLASTOMA AND NEPHROBLASTOMA | 190 |
| C. THERAPY OF RETINOBLASTOMA, RHABDOMYOSARCOMA AND OTHER SOLID TUMORS | 205 |
| D. PHARMACOKINETICS, THERAPEUTIC COMPLICATIONS AND PATIENT SUPPORTIVE CARE | 217 |
| **V. OTHER CLINICAL STUDIES ON PEDIATRIC NEOPLASMS** | 236 |
| A. COOPERATIVE GROUPS | 236 |
| B. BROAD CLINICAL PROGRAMS | 288 |
| C. EDUCATIONAL PROGRAMS | 314 |

**Investigator Index**

NOTE: If you are a Principal Investigator with a research project registered with the ICRDB, you are entitled to two complimentary subscriptions of CANCERGRAMS. If you are NOT receiving CANCERGRAMS, be sure to mention this in your next correspondence with the Program.

# CURRENT CANCER RESEARCH

## I. ETIOLOGICAL AND EPIDEMIOLOGICAL STUDIES OF PEDIATRIC NEOPLASMS

### A. FAMILIAL, GENETIC AND CONGENITAL FACTORS AND THE INCIDENCE OF CHILDHOOD CANCER

#### 1. FAMILIALITY OF CHILDHOOD CANCER

*Alvarez, A. M., Navarro Gonzalez, J., Ordonez, M. P., Delgado, A., Lanuza, I., Pineda, G., Martinez Caro, A., Garcia Valles, M. C.*, Hospital Infantil de la Ciudad Sanitaria Virgen del Rocio, Depto de Oncologia, *Ave. Manuel Siurot, Sevilla, Spain*

Numerous publications in recent years have demonstrated the familiality of childhood cancer. A study of the frequency of malignant and benign tumors in the families of 100-200 children aged 0-7 years, from the Andalucian and Extremaduran regions of Spain, who come to the cancer surgery department of the Children's Hospital, will be carried out. The family history of the patients will be investigated back through three to four generations, concentrating on the tumors which are most frequent in infancy. A parallel study of the family histories of children who come to the Children's Hospital with illnesses not related to cancer will be carried out simultaneously.

#### 2. FAMILIAL, CONGENITAL AND GENETIC FACTORS IN MALIGNANCY

*Mulvihill, J. J., Li, F. P., McKeen, E. A., Parry, D. M., Hassinger, D., Hanson, M. R., Hope, D., Meyn, S., Willis, R., Reardon, M.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Field Studies & Statistics Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Study of genetic diseases with neoplastic manifestations and detailed investigation of families with high risk of cancer may help detect environmental and genetic influences in carcinogenesis, especially when appropriate laboratory assays are used.

Besides results from our Clinical Studies Section and the Family Studies Unit of the Environmental Epidemiology Branch, laboratory reports were made on abnormal lymphocyte responses in four families with malignant melanoma complicating BK mole syndrome, an excess frequency of HLABw35 in 13 Hodgkin's disease families, and in vitro radiosensitivities in a family with acute myelogenous leukemia and a radiogenic rectal carcinoma. A monograph on neurofibromatosis was edited and a collaborative NIH clinical-laboratory investigation of neurofibromatosis begun. Various groups of patients who survived cancer were studied for reproductive performance. Syndromes that do or may predispose to cancer were discovered or further delineated. Various methods to stimulate similar research were used including guest lectures, literature reviews, and participation in committee activities.

#### 3. THE AMERICAN FAMILY LIFE STUDIES

*Wang, H. H., Grufferman, S., DeLong, E. R.*, Duke University, School of Medicine, Dept. of Community & Family Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

The American Family Life Assurance Company (AFL), a national cancer insurance company, has made its records available for epidemiological research. It currently has 2.7 million policies in force, approximately two thirds of which are family policies. Pathological reports to confirm diagnoses of cancer and detailed descriptions of treatment received are required for receipt of benefits or reimbursement. All this information is microfilmed. A series of studies will be based on these records. The first will be the determination of age- and sex-specific cancer incidence rates in the insured population to serve as the reference rates in the other studies. The second group of studies will be on the occurrence of cancer in spouse-pairs to assess the role of shared environment in the etiology of several cancers, such as Hodgkin's disease, colon, and genital and reproductive tract cancers. The third group of studies will investigate the risk of second primary cancers in relation to different types of therapy. Dose-response relationships will be evaluated for those therapies found to increase the risk of second primary cancers. Other studies will include examination of sibling aggregation in childhood cancer, re-evaluation of the 'cancer family' hypothesis and cancer incidence rates in specific occupational groups.

#### 4. EPIDEMIOLOGY OF CHILDHOOD CANCER

*George, S. L., Pratt, C. B.*, St. Jude Children's Research Hospital, Biostatistics Section, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

This general study will attempt systematic gathering of data from all children with malignant disease admitted to a large children's research hospital. The overall objectives are to characterize better the features of children with cancer and their families and to search for clues to etiology. Techniques to be used include the following: retrospective review of medical records; questionnaire/interview of families at diagnosis when possible; follow-up interviews and examinations for late effects, up-dates of initial information and progeny of long-term survivors; case-control studies where feasible. Over 300 newly diagnosed patients with cancer are admitted each year, mostly from the immediately surrounding, largely rural area. Areas to be systematically covered for all families include: socio-economic/occupational history, exposure to known carcinogens/pathogens (including ionizing radiation), previous diseases, other environmental factors and host factors (familial cancer, congenital abnormalities, etc.). An initial case-control study of children with colorectal cancer, using neighborhood controls, has begun.

#### 5. CLINICAL STUDIES SECTION, BOSTON, MASSACHUSETTS

*Li, F. P.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Studies Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The staff of Clinical Studies Section in Boston, Massachusetts, has sifted a large volume of clinical data to identify patients for etiologic studies. These unusual patients are usually found through attendance at clinical conferences and rounds, and through special referrals. With informed consent, epidemiologic studies are made of the environmental and genetic background and laboratory studies are performed to clarify biologic mechanisms of carcinogenesis. At present, several family aggregates of cancer are under study, e.g., Turcot's syndrome in two families; familial ureteral cancer, ataxia-pancytopenia syndrome, breast cancer-sarcoma syndrome. Also, a computerized Registry of Survivors of Childhood Cancer has been established through collaboration of the Clinical Studies Section with the Sidney Farber Cancer Institute. The 700 registrants represent approximately 2% of all survivors of U.S. childhood cancer in the last two decades. Patients in the series are being studied for second malignancies, cancer in close relatives, and genetic effects in progeny.

## 6. ETIOLOGY OF HUMAN CANCER

*Li, F. P., Miller, R. W., Fraumeni, J. F., Mulvihill, J. J., Bader, J. P., Zelnen, M.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Epidemiology Branch, *35 Binney St., Boston, Massachusetts,* 02115, United States of America

The objective is to study the epidemiology of human neoplasms and to develop etiologic hypotheses through close bedside observation of individual patients. Adult and pediatric cancer patients are interviewed for clues to the etiology of their cancer. Clues identified through the interviews are pursued in clinical and epidemiological studies. In addition, laboratory studies have been carried out in several families with strong histories of cancer to identify possible inherited defects or environmental risk factors.

## 7. SISTER CHROMATID EXCHANGE (SCE) IN CHILDREN WITH A MALIGNANT DISORDER

*Seshadri, R., Sutherland, G.,* Flinders University of South Australia, Flinders Medical Centre, Dept. of Haematology, *Bedford Park, S Australia 5042, Australia*

OBJECTIVE: 1. To analyze SCE rate in the lymphocytes of children with cancer and their relatives at the time of diagnosis. 2. To analyze SCE rate in children who have been treated with cancer chemotherapeutic agents.

APPROACH: Peripheral blood lymphocytes are cultured in the presence of bromodeoxyuridine for 3 days and SCE rate in the chromosome is analyzed.

PROGRESS: To date 40 children with various forms of malignancy have been analyzed. Children with Wilms' tumor who have been treated with actinomycin showed increased SCE rate compared to controls. No specific abnormality as yet has been found in newly diagnosed cases.

## 8. MUTAGENESIS IN CHILDHOOD LEUKEMIA AND CANCER

*Morley, A. A., Seshadri, R. S.,* Flinders University of South Australia, Flinders Medical Centre, Haematology Laboratory, *Bedford Park, S Australia 5042, Australia*

OBJECTIVE: To measure mutation frequency and fidelity of DNA repair in the lymphocytes from patients with childhood leukemia and cancer.

APPROACH: Mutation frequency in lymphocytes will be measured by determining the number of thioguanine resistant lymphocytes as assessed using autoradiography. Fidelity of DNA repair in lymphocytes will be measured by exposing lymphocytes to various mutagens, allowing time for expression, and then measuring mutation frequency. Study will be made of patients with childhood leukemia and cancer and of the families of such individuals.

## 9. MUTATION AND CANCER - IMPLICATIONS OF A MODEL FOR CHILDHOOD CANCER

*Strong, L. C.,* University of Texas, University of Texas System Cancer Center, Dept. of Pediatrics/Biology, *6723 Bertner Ave., Houston, Texas,* 77030, United States of America

This study involves study of childhood cancer with respect to hereditary and nonhereditary features, in an effort to characterize, at the clinical and cellular levels, genes which predispose to cancer. Patients are identified through systematic survey of medical records, and from referral from the departments of medicine and paediatrics. Family studies are undertaken for all patients. Patients and relatives are evaluated with respect to tumor type, tumor multiplicity, age at diagnosis, familial pattern, presence of associated tumors or congential anomalies and independent risk factors. In vitro studies or clinical examinations of high-risk relatives are conducted as appropriate.

## 10. CHROMOSOMAL STUDY OF PATIENTS WITH NEUROFIBROSARCOMA IN VON RECKLINGHAUSEN'S DISEASE

*Gomez, J., Rodriguez, H., Forero, E., Gutierrez, R., Rodriguez, C.,* Instituto Nacional de Cancerologia, Seccion de Cirugia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: Von Recklinghausen's disease is a congenital entity in which neurofibromas have a high probability of malignant degeneration. Chromosomal mapping of patients will be performed to look for the possibility of specific genetic alterations.

MATERIAL AND METHODS: All patients with confirmed diagnosis of neurofibrosarcoma in von Recklinghausen's disease and who display the symptoms of this disease will be studied. (Translated)

## 11. GENETIC STUDIES OF RETINOBLASTOMA AND THE RB-1 LOCUS

*Ferrell, R. E., Strong, L. C., Ricardi, V. M.,* University of Texas, Health Science Center at Houston, Graduate School of Biomedical Sciences, Center for Demographic & Population Genetics, *P.O. Box 20334, Houston, Texas,* 77025, United States of America

The objectives of this proposal are to determine the precise relationship between the genetic locus coding for the enzyme Esterase D and the RB-1 locus, defined by an interstitial deletion of chromosome 13, on human chromosome 13 by quantitative assays of Esterase D and karyotype analysis of members of families with multiple generations of retinoblastoma patients. To determine whether the quantitation of Esterase D is a useful tool in searching for deletions of chromosome 13 not visible during karyotype analysis, and to apply this to individuals with retinoblastoma in the absence of an obvious deletion. To search for evidence for the involvement of more than one genetic locus in the development of retinoblastoma by linkage analysis between RB-1 and a large battery of genetic markers as a test of the multi-hit hypothesis for childhood cancer.

## 12. THE GENETICS AND EPIDEMIOLOGY OF RETINOBLASTOMA

*Draper, G. J., Sanders, B. M.,* University of Oxford, Dept. of the Regius Professor of Medicine, Childhood Cancer Research Group, *9 Keble Road, Oxford OX1 3QG, United Kingdom*

The objectives of this study are: (1) To determine the incidence of second primary tumors, particularly osteosarcoma, among children surviving retinoblastoma; (2) to determine whether there is an increased incidence of other cancers, either in general or of certain specific types, among the parents of children with retinoblastoma; (3) to ascertain whether, as for certain congenital defects, the incidence of this disease is related to parental age; and (4) to examine associations between congenital defect, particularly mental retardation, and retinoblastoma. About 500 case of retinoblastoma have been ascertained through hospital, cancer registries and death certificates; epidemiological and familial data are also being collected.

## 13. GENETICS OF EMBRYONAL TUMORS

*Strong, L. C., Riccardi, V. M., Ferrell, R.,* University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Pediatrics/Biology, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

The objective of this study is to identify specific genes or chromosomal segments which may be involved in the etiology of embryonal tumors. Patients referred to the M.D. Anderson Hospital with childhood cancer and family history of childhood cancer, congenital anomalies, developmental delay, or multiple primary tumors, are candidates for study. It is anticipated that some 20 patients will be studied each year. Peripheral lymphocytes and, when present, tumors are reviewed for chromosomal aberrations detectable by metaphase and prometaphase banded (Giemsa, R. banding, etc.) preparations and/or by polymorphic biochemical markers. The frequency of IIp in about 100 patients with Wilms' tumor will be assessed.

## 14. GENETIC CONSEQUENCES OF CHILDHOOD CANCER

*Strong, L. C., Herson, J.,* University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Pediatrics/Biology, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

The objective of this study is to identify genetic effects of cancer and therapy, including both the primary factors predisposing to cancer which may lead to subsequent tumors in the patient or heritable tumors in offspring, and treatment-induced mutations which may lead to subsequent tumors or heritable disease in the offspring of patients who have had childhood cancers. A registry of long-term survivors of childhood cancer

and their offspring is being established, including data concerning congenital anomalies, predisposing conditions, family history, primary cancer treatment, and other medical or social history. Multiple factorial analysis of risk factors of second tumors and of genetic disease in the offspring will be undertaken.

### 15. CLINICAL CANCER GENETICS

*Strong, L. C., Anderson, D. E., Hsu, T. C., Pathak, S., Au, W.,* University of Texas, University of Texas System Cancer Center, Dept. of Pediatrics/Biology, *6723 Bertner Ave., Houston, Texas,* 77030, United States of America

The objectives of this study are to identify unusual familial aggregations of childhood cancers, associations of childhood cancer and congenital anomalies, or the occurrence of rare tumours in childhood for further aetiological study. Patients are referred from clinical departments. All cancers or other disorders in families under study are documented by medical records and/or vital statistics. Documented familial cases are compared with nonfamilial cancer cases with respect to age at onset, anatomical site, multiplicity of cancers, congenital and chromosomal abnormalities or other predisposing conditions. Within affected families, various clinical and genetic markers are being evaluated.

### 16. NIH INTER-INSTITUTE GENETIC CLINIC

*Parry, D. M., Mulvihill, J. J., Bader, J. L., McKeen, E. A., Gilman, P. A., Hassinger, D., Hanson, M.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Field Studies & Statistics Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The Genetic Clinic is a collabrative undertaking by researchers from 5 different institutes and the Clinical Center. Consequently, Clinic patients constitute a broad spectrum of genetic disease. The patient load during the Clinic's first year comprised 250 individuals representing 50 different diagnostic categories. Of these, 84 patients (33%) were seen by members of CEB. The Clinic provides a multidisciplinary setting in which to study unusual patients who either have cancer or an increased risk of developing malignancy. Patients are ascertained through special referrals from outside physicians and inhouse requests for etiologic consultations. With informed consent, the approach to the patient includes detailed physical examination, and, where applicable, epidemiologic studies of the environmental and genetic background and laboratory studies to clarify biologic mechanisms of carcinogenesis. Categories include patients with neurofibromatosis, a common autosomal dominant disorder that has an increased predisposition to cancer, patients with birth defects and cancer, families with childhood sarcomas and breast cancer in blood relatives, and any other families with an excessive occurrence of cancer of any type.

### 17. CONGENITAL ABNORMALITIES IN CHILDREN WHO DEVELOP MALIGNANT DISEASE

*Bithell, J. F., Kinnier Wilson, L. M.,* University of Oxford, Dept. of Biomathematics, *Pusey Street, Oxford, England, United Kingdom*

This is a retrospective analysis of data from the Marie Curie/Oxford Survey of Childhood Cancer Deaths between 1953 and 1970. Information on congenital abnormalities in the index children, control children and their respective sibs was obtained by interview and is now being collated and analysed to establish the nature of any associations between congenital abnormalities and malignant disease. The information on the sibs is especially valuable as a means of determining which observed associations may be of familial origin as opposed to being chance observations.

### 18. CONGENITAL MALFORMATIONS AND NEOPLASMS IN NEWBORNS AND INFANTS

*Hauge, M., Jensen, N. K., Haegerstrand, I., Kildeberg, P., Kristoffersen, K.,* Odense Universitet, Inst. of Clinical Genetics, *17 Winslowsvej, 5000 Odense C, Denmark*

A ten per cent sample of the population of Denmark is being followed from birth through infancy to provide incidence and prevalence figures for congenital malformations and malignant growths. Sources of information include: hospital case records, midwives' reports, death certificates and postmortem reports. Within the area selected all cases having been diagnosed as neoplasms will be traced. Basic population data are available in great detail.

### 19. DERMATOGLYPHICS IN CHILDHOOD NEOPLASIA

*Oorthuys, A. M., de Vaan, G. A., Haanen, C. A.,* Katholieke Universiteit Nijmegen, Dept. of Human Genetics, *Philips van Leydenlaan 25, Nijmegen, Netherlands*

OBJECTIVE: To characterize flexion creases and dermal configurations on palms and soles of patients with childhood neoplasia and of their first degree relatives.

APPROACH: Printing of palms and soles of pediatric patients with acute leukemia (AL) or with other neoplasms (malignant non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, brain tumors, Hodgkin's disease) and their relatives.

PROGRESS: Material has been extensively enlarged; results remain consistent with earlier reports. Association between resistance to childhood neoplasia and early fetal development is feasible in so far that among young patients with AL a relation seems to exist between good prognosis and absence of variant dermatoglyphic features. Correlation of dermatoglyphic variance, defects of purine- and pyrimidine-metabolism, and HLA-typing, among patients with childhood neoplasia and their relatives, is the objective of further study.

### 20. SYSTEMATIC DETERMINATION OF GENOTYPE OF TWINS AT BIRTH

*Derom, R. M., Thiery, M., Boelaert, R., Vlietinck, R.,* Rijksuniversiteit te Gent, School of Medicine, Dept. of Obstetrics, *Pintelaan 135, 9000 Ghent, Belgium*

Type, frequency and concordance of congenital malformation. Cancer epidemiology in monozygotic and dizygotic twins. Frequency of malignant conditions in twins which have been exposed to radiation in utero.

## B. IN UTERO EXPOSURE TO EXOGENOUS ESTROGENS AND OTHER AGENTS AND THE INCIDENCE OF CHILDHOOD CANCER

### 21. DELAYED EFFECTS OF INFERTILITY TREATMENT ON WOMEN AND THEIR OFFSPRING

*Ron, E., Lunenfeld, B., Menczer, J., Modan, B., Oelsner, G.,* Chaim Sheba Medical Center, Dept. of Clinical Epidemiology, *Bitan 27, Tel Hashomer, Ramat Gan, Israel*

The objectives of this study are: (1) to determine whether treatment for infertility leads to an increased risk of malignant neoplasms and total mortality in the treated women, and (2) to assess the risk of gross congenital malformations, abnormal sex ratio, malignant neoplasms and total mortality in the offspring of the treated women. The study group consists of all women treated for infertility between 1964 and 1975 at the Chaim Sheba Medical Center. It is estimated that approximately 1,000 women will be included in the study population. The frequency of study parameters will be studied in women receiving treatment with human menopausal gonadotropins, clomiphene and non-hormonal treatments, and the results compared, as well as correlated with age-ethnic standardized rates.

### 22. CANCER IN PERSONS EXPOSED TO EXOGENOUS ESTROGENS

*Falcier, F. W., Meigs, J. W., Flannery, J. R.,* Yale University, School of Medicine, Dept. of Epidemiology & Public Health, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

The purpose of this research is to estimate the range of cancer risk from prenatal exposure to exogenous estrogens among mothers and their exposed male and female offspring. Two matched control groups of unexposed mother-offspring pairs will be identified and the cancer incidence among these groups will be compared to that in the at-risk group. One group will be based on physician-matched controls, the second control group will be selected using Connecticut birth registration data. Cancer experience will be determined by linking the names of members of the cohorts to those of patients reported to the Connecticut Tumor Registry. All cancer sites will be considered, with particular attention paid to reproductive system cancers. To date more than 1,000 exposed mother-offspring pairs

and 1,000 physician matched control pairs have been identified and detailed information has been abstracted from their prenatal medical records. An additional 500 exposed pregnancies have been identified and data collection is in progress. Individual follow-up is being conducted for each mother and offspring in all cohorts.

### 23. ESTROGENS AND GENITAL ANOMALIES AND CANCER IN OFFSPRING

*Kaufman, R. H.*, Baylor College of Medicine, School of Medicine, Dept. of Obstetrics & Gynecology, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

OBJECTIVE: Identify and study offspring of women who received synthetic estrogens during pregnancy between 1943 and 1963. Repeat examinations at regular intervals, perform diagnosis and follow-up and treatment as necessary. Approximately 1,000 offspring are to be examined on this contract.

PROPOSED COURSE: The contractor will establish standard definition of eligibles and develop suitable approaches to elicit eligibles through information campaigns directed at physicians and the general public via mass media. Evaluation will be performed and reported.

PROGRESS: A total of 548 participants had been entered by March 1976. Of these, 519 are active participants, with 446 having documentation of DES exposure in utero. Chart reviewing by physicians in the Houston area has been the primary source of participants. Also, the health services at local universities have been used as an outreach to women students. Consent forms have been utilized.

### 24. ESTROGENS AND GENITAL ANOMALIES AND CANCER IN OFFSPRING

*Robboy, S. J.*, Massachusetts General Hospital, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

OBJECTIVE: A study of the incidence and natural history of genital tract anomalies and cancer in offspring exposed in utero to synthetic estrogens.

### 25. STUDY OF GENITAL TRACT ANOMALIES

*Decker, D. G.*, Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

The Contractor shall: Identify a population of approximately 1000 offspring (males and females) whose mothers received a synthetic estrogen during pregnancy; examine each individual in the population for the purpose of detecting congenital abnormalities or the presence of cancer; develop suitable treatment protocols for each particular diagnosis; and conduct a continuing data analysis, evaluation and assessment of this effort.

### 26. STUDY OF GENITAL TRACT ANOMALIES

*Townsend, D. E.*, University of Southern California, School of Medicine, Dept. of Obstetrics & Gynecology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

OBJECTIVES: Identify and study offspring of women who received synthetic estrogens during pregnancy between 1943 and 1963. Repeat examinations at regular intervals, perform diagnosis and follow-up and treatment as necessary. Approximately 1,000 offspring are to be examined on this contract.

PROPOSED COURSE: The contractor will establish standard definition of eligibles and develop suitable approaches to elicit eligibles through information campaigns directed at physicians and general public via mass media. Evaluation will be performed and reported.

PROGRESS: A total of 585 participants had been entered by March 1976. Of these, 508 are active participants, with 374 having documentation of DES exposure in utero. Prenatal record review process has been used to obtain participants. Consent forms have been utilized.

### 27. PRENATAL EVENTS AND CANCER RISK IN THE OFFSPRING

*Dukkers van Emden, D., Koppe, J. G., Peters, G.*, Universiteit van Amsterdam, Dept. of Neonatology, Wilhelmina Gasthuis, *Eerste Helmersstraat 104, 1054 EG Amsterdam, Netherlands*

The objective is to examine the relationship between use of anti-epileptic drugs or viral infection during pregnancy and cancer risk in the offspring. A follow-up study has been done of the outcome of 249 pregnancies in epileptic women undergoing treatment with anticonvulsants. The children were born between 1963 and 1977. Three children were stillborn, nine died subsequently. Postmortem examination in six cases showed multiple congenital abnormalities, no signs of malignancy. In the remaining group of 237 children, one boy, born in 1966, developed Hodgkin's disease (stage I) in 1973. His mother had used phenytoin, phenobarbital and primidone in high dosages during the entire pregnancy. No other malignancies were found in the group.

### 28. RISK OF CHILDHOOD CANCER FOLLOWING INTRAUTERINE EXPOSURE TO ANTIEPILEPTIC DRUGS

*Hiilesmaa, V. K.*, Helsingin Yliopisto, Dept. of Gynecology/Obstetrics, *Fabianinkatu 33, SF00290 Helsinki 29, Finland*

OBJECTIVE: The aim of the study is to investigate whether a mother's use of antiepileptic drugs during pregnancy is associated with an increased risk of childhood malignancies in her offspring.

APPROACH: A cohort of about 3000 children born to epileptic mothers in the years 1970-79 is identified through the files of the National Health Insurance and Pension Institution (Kansanelakelaitos) of Finland. Cases of childhood cancer among these children are identified by the standard reporting of new cancer cases to the Finnish Cancer Registry (Syoparekisteri). Incidence of malignancies among the children of epileptic mothers who have been on antiepileptic drugs during pregnancy is compared with the overall incidence of childhood cancer in Finland or with the incidence among a control cohort of children of non-epileptic mothers matched for age, area of residence, social class or other relevant factors.

### 29. PRENATAL EVENTS AND CHILDHOOD CANCER

*Munoz, N., Wald, N. J., Pasca, A.*, Centre International de Recherche sur le Cancer, Interdisciplinary Programme & International Liaison, *150 Cours Albert Thomas, 69372 Lyon Cedex 2, France*

This programme uses material from established prospective studies to assess the role of prenatal events in the incidence of congenital malformations. The Oxford study was started in 1972; by December 1977 a cohort of 18,000 had been assembled. The pregnancy records in this study contain information on illnesses during pregnancy and on exposure to drugs and chemicals; two or more antenatal serum samples and one postnatal sample were collected for each woman admitted to the study. The Hungarian study dates from 1975 and now consists of the records of 12,500 pregnant women. In this study antenatal specimens will also be available, in addition to the pregnancy records. The children born to women participating in either of these studies are being followed to identify those with congenital malformations or cancer. The occurrence of these diseases will be correlated with specific intrauterine exposures recorded in the pregnancy records, and the serum specimens and controls will be used appropriately.

### 30. NATIONAL SURVEY OF CHILDHOOD CANCERS

*Kinnier Wilson, L. M., Stewart, A. M., Draper, G. J., Waterhouse, J. A.*, Marie Curie Memorial Foundation, Epidemiology Unit, *The Chart, Oxted RH8 0TL, England, United Kingdom*

This long-standing retrospective survey was originally started in Oxford by Dr. A. Stewart in 1953 to study the etiology of childhood cancers. It consists of interviews with the parents of children under 16 dying of cancer or leukemia in the United Kingdom and with parents of control children matched for age, sex and district; antenatal information is confirmed by application to clinics and doctors, and the case child's medical history is followed up through general practitioner and hospital notes. Surviving children have similarly been interviewed and followed up since 1962 by means of the regional cancer registries. In the past extensive studies have been made of the relation of obstetric low-level radiation to the increased risk of the child later developing neoplasia. The effect of viral diseases during pregnancy has also been found to increase the risk, but less convincingly. Present projects include: (1) A study of the effects of the use of drugs and ultrasound during pregnancy, and of the possible role of these agents in the etiology of childhood cancers; (2) a study of parental occupations and their possible relationship to the etiology of childhood cancers; (3) a study of congenital defects found in children who later develop cancer

or leukemia, and congenital defects in their siblings, together with a similar study of defects in matched control children and their siblings; (4) a study of second primary tumors occurring in children after cure of their initial cancer with special attention to the effect of radiation and genetics.

### 31. ROLE OF INTRAUTERINE INFECTIONS IN CHILDHOOD CANCER

*Pacsa, A. S., Pejtsik, B. A., Angyal, T.,* Pecsi Orvostudomanyi Egyetem, Microbiology Inst., Virology Unit, *Szigeti Utca 12, 7643 Pecs, Hungary*

The aetiological background of childhood cancer may partly be traced by testing serum samples collected from pregnant women. Cooperating with Pregnancy Care Units, the project covers approximately 5,000 pregnant women a year. At least three serum samples are collected for each pregnancy and 6,000 pregnancies have been covered so far. It is planned to obtain such serial samples from 15,000 pregnancies and compare antibody titres (viral and bacterial) in mothers of children who subsequently developed cancer with antibody titres in other mothers. The testing of samples to determine the possible effect of pregnancy on humoral immunity has already started. Part of the work has been published.

### 32. A CASE-CONTROL STUDY ON CANCER AND MALFORMATION IN CHILDHOOD

*Puntoni, R., Vercelli, M., Panizza, A., Santi, L., Bruzzi, P. A.,* Universita degli Studi di Genova, Istituto de Oncologia, Dept. of Epidemiology, *Viale Benedetto 15, Pad. B, 16132 Genoa, Italy*

The aim of this investigation is to study the relationship between cancer and malformation and maternal exposure to suspected carcinogens (event or factor) during pregnancy. All the cases of cancer and malformation seen at Gaslini Hospital in Genoa during the period 1972-78 (about 500) have been collected. A random sample of children of the same age and sex with different diseases seen at the same hospital will constitute the control group.

### 33. U.S. CANCER MORTALITY SURVEY

*Mason, T. J., Hoover, R. N., Blot, W. J., Stephenson, B. L., Ramsbottom, R. I., Blair, A. E., Fraumeni, J. F., Pickle, L. W.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Population Studies Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The objective of this study is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigation to test specific etiologic hypotheses. Possible prenatal origins of childhood cancer are being investigated by focusing on potential exposures realized by the pregnant mother. The rising rates of myeloma in blacks suggest genetic and environmental factors that need to be tested in analytic epidemiologic studies. Analysis of non-Hodgkin's lymphoma at the county level for 1950-1975 detected associations with higher social class and also large percentages of residents of Russian and Greek descent. Changes in age-specific rates for breast cancer appear related to the changing patterns of childbearing among young adult women of the first two-thirds of this century. Analyses of changing patterns in the rates of thyroid cancer in Connecticut detected findings consistent with the use of radiation therapy from the early 1920's to the late 1950's.

BIBLIOGRAPHIC REFERENCES: Blattner, W.J., Mason, T.J., and Blair, A.: Changes in mortality rates from multiple myeloma. New Engl. J. Med. 302: 814-815, 1980. Blot, W.J., and Fraumeni, J.F., Jr.: Lung cancer mortality in the United States: Shipyard correlations. Ann. N.Y. Acad. Sci. 330: 313-315, 1979.

### 34. ENVIRONMENTAL EPIDEMIOLOGY

*Brown, S. M., Everson, R. B., Sandler, D. P., Rogan, W., Wilcox, A. J.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Environmental Health Sciences, Biometry Branch, *P.O. Box 12233, Research Triangle Park, North Carolina,* 27709, United States of America

This project involves a number of related studies of chronic disease or cancer epidemiology. It includes a preliminary investigation into the etiology of Reye's Syndrome; an investigation into the relationship of maternal smoking and childhood cancer; an investigation into the relationship of selenium and other trace elements to skin cancer; an investigation of occupationl exposure to hair dyes and the occurrence of death from breast cancer; and an investigation of the relationship of estrogen receptors to other known risk factors for breast cancer.

### 35. STUDIES OF REPRODUCTIVE EFFECTS OF LOW-LEVEL RADIATION EXPOSURE

*Sandler, D. P., Brown, S. M., Hoel, D. G.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Environmental Health Sciences, Biometry Branch, *P.O. Box 12233, Research Triangle Park, North Carolina,* 27709, United States of America

A series of four epidemiologic studies is intended to evaluate the possible effects on human reproduction of low-dose radiation exposure. The individual studies are designed to specifically examine the relationship of radiation exposure to birth defects, spontaneous abortion, fetal and infant death, childhood cancer and human growth and development. Each of the studies focuses on different possible reproductive outcomes, but the studies and the study populations overlap and will provide complementary data. Two general populations are being studied. These are a cohort of nuclear workers (female workers and wives of male workers) who are occupationally exposed to low levels of radiation (external and internal exposures), and a cohort of births to nuclear workers. Data for all segments of the study will be collected using medical records, vital records, subject interviews, employment records or a combination of these sources.

### 36. SHORT-TERM VARIATION IN PRE-NATAL CANCER RISK

*Bithell, J. F., Draper, G. J.,* University of Oxford, Dept. of Biomathematics, *Pusey Street, Oxford, England, United Kingdom*

An analysis has been undertaken in which all deaths from malignant disease of British children between 1953 and 1971 have been tabulated by month of birth and age at death. Comparative 'expected' numbers have been computed with allowance for survey coverage, cohort size and secular trends. A program has been developed which is designed to correlate these series of observed and expected numbers in an appropriate manner with any time-varying factor of interest. A study of the temporal association with influenza and poliomyelitis incidence has been completed; the data are available for the analysis of any monthly observations that may be of etiological interest or significance.

## C. IATROGENIC EXPOSURE TO RADIATION AND DRUGS AND THE INCIDENCE OF CHILDHOOD CANCER

### 37. RELATIONSHIP BETWEEN LEUKEMIA AND EXPOSURE TO DIAGNOSTIC RADIATION

*Majle, T., Landau, E. Z., Lundin, J.,* National Inst. of Hygiene, Dept. of Radiation Protection & Radiobiology, *24 Chocimska St., 00791 Warsaw, Poland*

The Tri-State Leukemia Study in U.S.A., 1962-1963, showed an excess of leukemias in adult males associated with an increased frequency of x-ray examinations. The purpose of the present study is to validate the results of the Tri-State Leukemia Study and to estimate exposure and dose of x-rays in 1,000 leukemia patients and in 1,000 controls chosen by random sampling from the Polish population. A retrospective survey provides information on the number and kind of x-ray examinations during the past 20 years. Information obtained from patients and controls is confirmed in hospitals, polyclinic records and archives. Exposure and dose of x-rays will be compared in both groups. A pilot study in Warsaw of 225 leukemia cases and 419 controls was completed in 1978. Some of the results show that the radiation load in leukemia patients may be higher than in relevant control groups. The results in children seem to indicate that children with leukemia were subjected to a higher number of x-ray examinations than the controls.

## 38. RADIATION RISK IN ISRAELI CHILDREN WITH TINEA CAPITIS

*Modan, B.*, Chaim Sheba Medical Center, *Bitan 27, Tel Hashomer, Ramat Gan, Israel*

OBJECTIVE: Update a list of persons treated for tinea capitis between 1949-1960 and obtain information about subjects who developed benign tumors or cancer of the thyroid, brain, parotid gland, breast, bone, lung, esophagus, leukemia, and lymphoma. This information will then be compared with that on a control group. The analysis will be done by NCI investigators at the end of the project.

## 39. RADIATION CARCINOGENESIS

*Neumeister, K.*, Staatliches Amt fuer Atomsicherheit und Strahlenschutz, *Waldowallee 117, 1157 Berlin, German Democratic Republic*

Epidemiological analyses are undertaken of radiation-induced carcinoma and leukemia following diagnostic or therapeutic administration of ionizing radiation, including pre- and postnatal exposure in children, and of radiation-induced cancer in multiple primary malignant tumors in the German Democratic Republic.

## 40. LATE EFFECTS IN CHILDREN AND ADULTS OF 224RA INJECTIONS

*Spiess, H., Mays, C. W., Korhaz, J.*, Ludwig Maximilians Universitet Munchen, Kinderpoliklinik, *Pettenkoferstrasse 8a, 8000 Munich 2, Federal Republic of Germany*

Nine hundred patients treated with 224Ra for tuberculosis, ankylosing spondylitis and other diseases, mainly during the years 1946-1951, have been followed up over a 30-year period. Fifty cases of bone sarcomas and 4 cases of chondrosarcomas have been found, of whom 36 cases had been treated with 224Ra as juveniles and 18 as adults. Follow-up continues.

## 41. HUMAN RADIATION CARCINOGENESIS STUDY

*Woodard, E. D., Hempelmann, L. H., Shore, R., Odoroff, C., Cooper, R., Goh, K., Nitzkin, J. L.*, University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This application proposes continuation of long-term prospective studies of three well-defined populations irradiated for benign conditions: (1) persons whose thymus glands were irradiated in infancy; (2) persons given x-ray and/or radium treatments for hypertrophy of adenoidal tissue during childhood; and (3) women whose breasts were treated with x-rays for acute post-partum mastitis. The objective of the program is to determine the risk of radiation-induced disease (neoplasia, autoimmune and psychiatric illness) with particular attention to the dose-response relationship for neoplastic disease. A second objective is to detect (by periodic mammographic-thermographic screening) and treat early cases of breast cancer in a high-risk population (mastitis-irradiated series). Additionally, findings in the screening program will be evaluated for predictive significance.

The health of the irradiated subjects and their non-irradiated sibling controls is followed by mailed health questionnaire. Significant illnesses and operations are verified with the attending physician and/or hospital. Sections of neoplasms of selected sites (breast, thyroid, and salivary glands) are requested for review. The breast-irradiated women and eligible controls (NCI guidelines) will be offered annual mammographic-thermographic screening. Laboratory studies of B and T lymphocytes will be conducted on selected individuals in the thymus series. Additional dosimetry calculations will be performed for selected tissue sites in the head-irradiated series (thyroid, pituitary, and salivary glands) and thymus-irradiated series (breast tissue).

## 42. LATE EFFECTS OF IRRADIATION OF ENLARGED THYMUSES IN CHILDREN

*Albert, R. E.*, New York University, School of Medicine, Dept. of Environmental Medicine, *100 Washington Sq. E., New York, New York,* 10003, United States of America

This is part of a broader project. A summary of this subproject is not available.

## 43. FOLLOW-UP STUDY OF PERSONS WHO HAD I 131 AND OTHER DIAGNOSTIC PROCEDURES DURING CHILDHOOD

*Hamilton, P. M.*, U.S. Dept. of Health & Human Services, Public Health Service, Food & Drug Admin., Bureau of Radiological Health, *5600 Fishers Ln., Rockville, Maryland,* 20857, United States of America

The objective is to assess the risk of development of thyroid neoplasms following exposure to I 131 by evaluating the thyroid neoplasm experience in young adults who received diagnostic I 131 during childhood, compared to the experience in a similar group of unexposed young adults and a group of unexposed siblings.

## 44. PARATHYROID DISEASES ASSOCIATED WITH IRRADIATION

*Tamura, K., Shimaoka, K., Spaulding, S., Shedd, D.*, Roswell Park Memorial Inst., Dept. of Medical Oncology, *666 Elm St., Buffalo, New York,* 14263, United States of America

There have been scattered reports showing that parathyroid adenoma and hyperplasia with hyperparathyroidism were associated with irradiation to the head and neck areas for benign diseases in childhood. To delineate this relation 50 documented cases with parathyroid adenoma or hyperplasia are being surveyed by mail questionnaire. The prevalence of hypercalcemia and hyperparathyroidism in more than 1,000 cases from the thyroid screening program where all that patients had radiation therapy for benign diseases in childhood or young adulthood, and in 300 patients with malignant lymphoma who have been treated with radiation therapy to the neck area, is also being examined.

## 45. LONG-TERM FOLLOW-UP OF CHILDHOOD CANCER SURVIVORS

*Draper, G. J., Heasman, M. A., Marsden, H. B., Harnden, D. G.*, University of Oxford, Dept. of the Regius Professor of Medicine, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

There is considerable concern about possible long-term effects of radiotherapy and chemotherapy used in treating children with cancer, including the induction of second primary tumors. It has also been suggested, though at present direct evidence is lacking, that improvements in survival for certain categories of tumor, and the subsequent increase in the number of children born to survivors, will lead to the recognition that there is a genetic component in the aetiology of some of the cancers of childhood comparable to that for retinoblastoma. The Childhood Cancer Research Group is coordinating a collaborative study which will eventually include records of about 6,000 children who have been treated for cancer and survived for at least three years. These survivors will be followed up to determine the incidence of second tumors and also the incidence of abortions, stillbirths, congenital defects and malignant disease among their children. For children treated in Scotland, subsequent hospital admissions, school health records and other medical records are being studied and compared with corresponding records for a sample of controls, using record linkage. Various other long-term effects may be studied for cases from particular centres. It is planned also: (1) To carry out laboratory studies including hematological studies, cytogenetics and possibly measurement of immunoglobulins for some of the cases included in the study and (2) to establish a pathology registry for children in whom second primary tumors occur.

## 46. FOLLOW-UP OF PATIENTS TREATED FOR MALIGNANT DISEASE

*Alderson, M. R., Alberman, E., Peckham, M. J.*, Inst. of Cancer Research, Division of Epidemiology, *Clifton Ave., Sutton SM2 5PX, England, United Kingdom*

This study will follow adolescents and young adults treated with increasingly powerful schedules to quantify the mortality from second malignancies and to check whether there is any evidence of a carcinogenic or teratogenic effect following conception. For both these groups of patients the original medical records will be abstracted; this will include detailed data on initial and subsequent treatment. Where patients have been followed until death, the cause of death will be obtained, whilst those known to be alive will be included, particular effort being made to trace patients presently lost to follow-up. Survivors

from adolescence will be interviewed when they have reached child-bearing age, and a marital history will be obtained including data on any conception that occurs. Information about miscarriage, stillbirth, or children born with congenital abnormalities will be sought; liveborn children will be followed to identify the incidence of malignancy.

### 47. CESSATION OF THERAPY IN CHILDHOOD LEUKEMIA IN THE NORDIC COUNTRIES

*Moe, P. J., Nygaard, R.*, Universitetet i Trondheim, Dept. of Pediatrics, *7000 Trondheim, Norway, Norway*

All cases of childhood leukemia in the 5 Nordic countries with cessation of therapy before January 1, 1978 have been registered. Yearly follow-ups have also been performed on all the cases taken off therapy. Attempts will also be made to obtain information on all cases of childhood leukemia diagnosed in the 5 Nordic countries since 1963. The purpose of this study is to determine the incidence of long-term survivors of acute childhood leukemia in the 5 Nordic countries, particularly those off therapy and without relapse.

### 48. LATE EFFECTS OF CANCER TREATMENT IN CHILDREN INCLUDING SECOND MALIGNANT NEOPLASMS - CHILDREN'S INTERNATIONAL CANCER INVENTORY

*Meadows, A. T., Banfi, A. D., Voute, P. A., Baum, E. S., D'Angio, G. J., Evans, A. E., Jenkin, R. D., Morris Jones, P. H., Newton, W. A., Siegel, S., Green, D.*, University of Pennsylvania, Children's Hospital of Philadelphia, *34th St. & Civic Ctr. Blvd., Philadelphia, Pennsylvania,* 19104, United States of America

As treatment for childhood cancer was becoming more successful and survivors were increasing, an interest developed in studying these children for late effects to organ systems of radiation and chemotherapy. Also of interest was the rate of second tumors in these survivors, whether treatment-related or not. Begun in 1972 at three pilot institutions, the study has been expanded to include children with cancer at 13 institutions, particularly with reference to: (1) the relationship of second malignant neoplasms (SMN) to therapy and other aetiological factors, (2) the incidence of SMN, (3) histopathology of SMN (4) survival of patients with SMN, (5) unusual tumors in children with cancer, (6) congenital anomalies in patients, (7) data regarding siblings and other family members for cancer and congenital defects, and (8) other deleterious sequelae encountered in patients cured of cancer in childhood. All studies are now active, including a case-control study of the 200 SMN in our registry to 1979.

### 49. SURVIVORS OF CHILDHOOD CANCER

*Li, F. P., Miller, R. W., Mulvihill, J. J., Fraumeni, J. F., Bader, J. P., Zelnen, M.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Epidemiology Branch, *35 Binney St., Boston, Massachusetts,* 02115, United States of America

A registry has been established of 5-year survivors of childhood cancer. To date, 600 patients have been enrolled. These patients and their progeny are being followed for development of new tumors and for evidence of late complications of cancer therapy. The study includes the physiological, psychological, oncogenic and genetic sequelae of successful cancer therapy in man.

### 50. STUDY OF ONCOGENESIS AND LATE EFFECTS OF CANCER THERAPY

*Meadows, A. T.*, Children's Hospital of Philadelphia, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania,* 19104, United States of America

OBJECTIVES: Obtain the necessary permissions to allow the EEB access to records of children with second cancers in all thirteen collaborating LESG hospitals, as well as permission to assess record systems for the selection of controls. Locate records (e.g., card files, computer listings) from which rosters of all long-term survivors of childhood cancer can be selected from each of the thirteen collaborating centers. Controls will be selected by the EEB from these rosters. Abstract information from the rosters of long-term survivors of childhood cancer following the study.

### 51. CASE CONTROL STUDY ON THE EFFECTS OF ANTI-MALARIALS IN THE ETIOLOGY OF BURKITT'S LYMPHOMA

*Sadoff, L., Bobrowsky, R.*, Kaiser Foundation Hospital, Dept. of Medicine, *4867 Sunset Blvd., Los Angeles, California,* 90027, United States of America

A case-control study testing the hypothesis that antimalarial drugs may influence the onset of Burkitt's lymphoma is under way in Kenya. To date 41 cases of Burkitt's lymphoma and 36 controls coming from the same geographical area and matched for age and sex have been studied. Of the children with Burkitt's lymphoma 46.3% had received no antimalarials in the two-year period preceding the onset of illness. All of the control cases had received such drugs during the same period, suggesting that antimalarials may protect against Burkitt's lymphoma.

### 52. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND THEIR OFFSPRING

*Hassinger, D., Myers, M. H.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Epidemiology Branch, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The Biometry and Clinical Epidemiology Branches of the National Cancer Institute intend to study morbidity in childhood cancer survivors and their offspring in California, Connecticut, Iowa, Kansas and Texas. The study will pay specific attention to effects of heredity and cancer treatment, looking especially at infertility in cases, and at birth defects and cancer in offspring.

### 53. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND OFFSPRING

*Holmes, F. F.*, University of Kansas, Medical Center, School of Medicine, Dept. of Medicine, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

OBJECTIVES: Provide information to, and elicit support of, local physicians hospitals concerning the study, where necessary. Identify a cohort of cases with characteristics as follows, with or without the aid of ERG case listings, from the local tumor registry records: histologic confirmation of malignant disease; diagnosis prior to age 19; survival of at least five years after diagnosis; and attainment of age 18 by time of death or last follow-up. Prepare a tape of available demographic and medical data on the identified cohort of cases and transmit this information to NCI.

### 54. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND OFFSPRING

*Strong, L. C.*, University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

OBJECTIVE: Provide technical and professional support to the Biometry and Clinical Epidemiology Branches necessary to identify, locate, contact and interview cases of childhood cancer survivors and controls, and collect and abstract selected medical and vital records for these individuals (following procedures detailed in individual registry task outlines).

### 55. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND OFFSPRING

*Meigs, J. W.*, Yale University, School of Medicine, Dept. of Epidemiology & Public Health, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

OBJECTIVES: Provide information to, and elicit support of, local physicians and hospitals concerning the study, where necessary. Identify a cohort of cases with characteristics as follows, with or without the aid of ERG case listings, from the local tumor registry records: histologic confirmation of malignant disease; diagnosis prior to age 19; survival of at least five years after diagnosis; and attainment of age 18 by time of death or last follow-up. Prepare a tape of available demographic and medical data on the identified cohort of cases and transmit this information to NCI.

**56. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND OFFSPRING**

*Latourette, H. B.*, University of Iowa, School of Medicine, Dept. of Preventive Medicine & Environmental Health/Radiol., *Oakdale, Iowa*, 52319, United States of America

OBJECTIVES: Identify, locate, contact, and interview cases and controls, and collect and abstract selected medical vital records for the study of 'Morbidity in Childhood Cancer Survivors and Their Offspring.'

**57. MORBIDITY IN CHILDHOOD CANCER SURVIVORS AND OFFSPRING**

*Austin, D. F.*, State Dept. of Health Services, *1450 Broadway, Oakland, California*, 94612, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

## D. DEMOGRAPHIC AND OTHER ETIOLOGIC FACTORS AND THE INCIDENCE OF SPECIFIC CHILDHOOD CANCERS

### 1. LEUKEMIA AND LYMPHOMA

**58. INCIDENCE AND GEOGRAPHICAL DISTRIBUTION OF CHILDHOOD LEUKEMIA IN THE NETHERLANDS 1972-1980**

*Van Zanen, G. E.*, Stichting Nederlandse Werkgroep Leukemie bij Kinderen, c/o Juliana Kinderziekenhuis, *Dr. van Welylaan 2, P.O. 60604, The Hague, Netherlands*

Since 1972 more than 95% of all new leukemia cases in children have been registered. This was done primarily to enroll new patients in clinical trials. In all the patients the Dutch Childhood Leukemia Study Group (DCLSG) has, as a central reference laboratory, confirmed the diagnosis on bone marrow aspirates, using the FAB (French-American-British Cooperative Group) classification. This patient material will now be analyzed in order to obtain a geographical map of incidence and distribution. Additional data will be obtained. The 'map' can be used to study relationships between environmental factors (air pollution, quality of drinking water, etc.) and leukemia incidence. Any possible clustering of cases will be traced.

**59. EPIDEMIOLOGY AND CLUSTERS OF TUMORS IN CHILDHOOD, FREQUENCY AND GEOGRAPHICAL DISTRIBUTION**

*Bilek, O., Vrba, M. O., Kubikova, A. J., Trnka, A.*, Inst. of Pediatric Research, *Cernopolni 9, Brno 66262, Czechoslovakia*

OBJECTIVES: In 1960-1968, 104 cases of childhood leukemia were observed in South Moravia. A significant clustering in space (0-12 km distance) and time (0-1, 0-2 years) was found (Blut, 21, 180-185, 1970). We intend to continue this study as these population groups, which could be regarded as genetic isolates, are very suitable for comparative studies of genetic factors. The main object of the study will be: (1) To register all cases of childhood leukemia from 1969 onwards; (2) to compare the previous (1960-1968) and the new (1969-1980) results; (3) to study the families with malignancy genealogically; and (4) to study the influence of environmental factors on the incidence of leukemia, if any.

**60. A STUDY OF CHILDHOOD LEUKEMIA IN NORTH WEST ENGLAND 1954-1977**

*Birch, J. M., Marsden, H. B., Swindell, R.*, University Hospital of South Manchester, Dept. of Epidemiology & Social Research, *W. Didsbury, Manchester M20 8LR, England, United Kingdom*

The annual incidence of leukemias of various cell types recorded by the Manchester Children's Tumor Registry during the period 1954-1977 has been analysed and the incidence of acute lymphoid leukemia has shown a significant increase. The data are currently being analysed to determine whether this increase is concentrated in any particular group. Factors being studied include age, sex, white cell count at presentation, social class and socio-economic group. Geographical studies are also being carried out to determine incidence trends in different parts of North West England and any association with features specific to a given area. A prospective case-control study of possible etiological factors (with emphasis on genetic and other pre-natal factors) will begin early in 1980. Controls will be selected from the population and matched for age, sex and race.

**61. CHILDHOOD LEUKEMIA IN NORWAY 1963-1979**

*Moe, P. J., Johansen, O. J.*, Universitetet i Trondheim, Dept. of Paediatrics, *7000 Trondheim, Norway, Norway*

Information about all cases of childhood leukemia diagnosed in Norway during the period 1963-1979 has been collected by contacting hospitals, particularly all pediatric departments, and for the first years - all the departments of internal medicine as well. Information has also been obtained from the National Cancer Registry as cancer registration is compulsory in Norway. Information was obtained as to the type of leukemia, year of diagnosis and survival time. The first part of this study has already been published. The aim of the second part of this study is to register all current cases of childhood leukemia with emphasis on cell-type, treatment regimen, results of therapy, and possible sequelae of the use of intermediate dose levels of methotrexate for almost all cases of lymphocytic leukemia diagnosed in Norway after 1975.

**62. EPIDEMIOLOGY OF LEUKEMIA AND ALLIED DISORDERS IN WESTERN AUSTRALIA**

*Dougan, L. E., Matthews, M. L.*, Cancer Council of Western Australia, Leukaemia & Allied Disorders Registry, *184 St. George's Terr., Shenton Park, Perth, W. Australia 6000, Australia*

Patients have been notified to the Leukemia and Allied Disorders Registry in Western Australia since 1959. Further registrations were made by search of hospital morbidity indices, pathology and hematology department records and death certificate scrutiny. For patients prevalent in the period 1960 to 1969 the diagnoses were confirmed or otherwise determined by a diagnostic group of pathologists and hematologists after review of clinical and pathological material. Epidemiological and clinical data have been collected for those patients with confirmed diagnoses and incidence and mortality rates have been calculated by sex, age and geographical area. Other data collected include irradiation exposure, drug ingestion, past medical history, family history, occupation, domicile, birth order, family size, parental ages, presence of other malignancy or congenital malformations, autopsy findings and death certification. Follow-up study is continuing in order to complete survival figures and data on the development of other malignancies. Since 1969 the registration of patients has continued but diagnoses are accepted without confirmation by the diagnostic group and less detailed epidemiological information is recorded. Copies of tabulations from the 1960-1969 survey are available on request.

**63. EPIDEMIOLOGICAL STUDY OF ACUTE CHILDHOOD LEUKEMIA (ABBREV)**

*Zannos Mariolea, L., Haidas, S., Dendaki Svolaki, C., Tzortzatou, F.*, University of Athens, Blood Research Lab., Dept. of Pediatrics, *Odos Panepistimiou 30, Athens 608, Greece*

Retrospective studies of acute childhood leukemia in Greece have shown an increased occurrence of new cases during the spring months and a significant yearly variation in the percentage of non-lymphoblastic forms. The main objectives of the present study are: (1) Characterization of the seasonal distribution of acute lymphoblastic leukemia (ALL) and acute non-lymphoblastic forms; (2) search for clustering of cases in space and time and clustering in time of cases with ALL which have a leukocyte count over 20,000 per mm3; (3) determination of the frequency of occurrence of the chloromatous form of acute leukemia (this variant is increased in Africa and Turkey); (4) estimation of frequency of leukemias, lymphomas, neuroblastomas and other malignant tumours among hospital admissions and of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and beta-thalassaemia trait among children with acute leukemia. Do these traits confer increased resistance against acute leukemia?

**64. EPIDEMIOLOGICAL STUDY OF ACUTE LEUKEMIA IN ADULTS AND CHILDREN (ABBREV)**

*Parker, J. E., Boldt, W.*, Lion's Gate Hospital, *E. 13th St., Vancouver, British Columbia*, V7L 2L7, Canada

In a retrospective study, an association between cases of acute leukemia in some adults and between other cases of leukemia in childhood or in other adults has come to light within the

suburban community of North and West Vancouver, there being a variable and sometimes long latent period between cases. A prospective questionnaire study of all newly diagnosed cases of acute leukemia within the above suburban community is being carried out, attempting to define a relationship between cases as to time, place and person. This is considered under the following headings: date of diagnosis, age, sex, duration of symptomatology, family history of malignancy, contact with other cases of lymphoreticular malignancy in family or friends, addresses and change of address (domestic and employment) within the above community, exposure to domestic animals. It is proposed to compare these findings with data on age matched controls i.e. non-leukemic cases admitted to Lion's Gate Hospital.

### 65. EPIDEMIOLOGY OF ACUTE CHILDHOOD LEUKEMIA

*Szklo, M., Tonascia, J. A., Gold, E., Kaplan, E., Gordis, L.,* Johns Hopkins University, School of Hygiene & Public Health, Dept. of Epidemiology, *615 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

Malignant diseases are the second leading cause of death in U.S. children, with leukemia accounting for about 30% of all childhood cancer deaths. Although a number of factors have been implicated in the etiology of childhood leukemia, including ionizing radiation and chemical agents, the etiology of most childhood leukemias remains unexplained. This case-control study aims to assess environmental influences in childhood leukemia, including factors which may act in utero or in early life. The study population consists of children identified in three metropolitan areas in the U.S. (Baltimore, Philadelphia, and Washington, D.C.). Three groups of about 50 children were individually matched by age, sex, race and hospital of diagnosis: children with acute leukemia, children with other malignancies, and children without malignancies. Interviews have been conducted among parents of these children, and data are now being analyzed.

### 66. ENVIRONMENTAL EXPOSURES AND CHILDHOOD LEUKEMIA

*Pendergrass, T. W.,* Children's Orthopedic Hospital & Medical Center, Division of Hematology & Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

Little is known of the role of parental occupational exposures or perinatal drug ingestion in the subsequent development of childhood acute lymphocytic leukemia. This study has two goals: a) development of a method for obtaining information on parental occupational and perinatal drug exposures, and b) testing of this method on parents of children diagnosed as having acute lymphocytic leukemia, between 1972 and 1979, in the State of Washington. Cases have been identified in the three major hospitals treating children with cancer in the State. For each case a hospital control has been selected to attempt to control for any differences in recall between parents of ill and presumably well children. General population controls will be obtained by use of a random digit dialing method. To date, 80% of case parents have been interviewed. Occupational data include a detailed review of occupational history and review of each job-related exposure. A detailed review of perinatal drug ingestion is obtained.

### 67. CHILDHOOD LEUKEMIA - ABELSON VIRUS

*Nathan, D. G.,* Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts,* 02115, United States of America

The overall focus of this program is directed toward a better understanding of cellular regulation. The individual components of the program are: (1) Bone marrow transplantation with reference to histocompatibility antigens not linked to HLA, autocytotoxic cells, and immunocompetence of transplant recipients; (2) suppressor cells; (3) human serum growth factor isolated from platelets; (4) murine virus transformation in vitro and in vivo; (5) regulation of RNA metabolism by growth factors and drugs; and (6) differentiation in erythroid culture systems.

### 68. EPIDEMIOLOGY OF LEUKEMIAS AND MALIGNANT LYMPHOMAS IN GUJARAT

*Shah, P. M., Baboo, H. A., Shah, A. K., Patel, N. L.,* Gujarat Cancer & Research Inst., Chemotherapy & Medical Unit, *New Civil Hosp. Campus, Ahmedabad 380016, Gujarat State, India*

There are very few epidemiological studies of leukemias and lymphomas available from India. The aim of this study is to evaluate the profile of these disorders in Gujarat State. 35 percent of Hodgkin's disease patients are in the pediatric age group and acute myeloid leukemia is common, whereas chronic lymphatic leukaemia is very rare. 900 cases had been collected by December 1978 and case collection continues.

### 69. ANIMAL CONTACTS IN YOUNGER VICTIMS OF HODGKIN'S DISEASE AND LEUKEMIA

*Doerken, H., Kuse, Grasedyck, Garbrecht, Stolzenbach, Frey, Guenther,* Universitat Hamburg, Medizinische Facultat, First Medical Clinic, *Martinistrasse 52, 2000 Hamburg 20, Federal Republic of Germany*

In the age-group 15-19 years 84 cases of Hodgkin's disease have been found in the State of Hamburg and Northern Germany during the last 10 years. Cases will be compared with controls with particular reference to contact with animals and the occupation of the parents. In a more rural area (Oberallageu/Bavaria) 191 death from leukemia occurred during the period 1959-1974. Animal contacts were analysed. An unexpected risk factor was prior use of chloramphenicol. 440 deaths from leukemia in the purely urban area of Hamburg North are now being analyzed and compared with data on controls. First results confirm the rarity of clustering.

### 70. STUDY OF ANIMAL CONTACTS IN LEUKEMIA

*Kessler, I. I., Pabon, H., Lin, R. S.,* University of Maryland, Baltimore Professional Schools, School of Medicine, Dept. of Epidemiology & Preventive Medicine, *655 W. Baltimore St., Baltimore, Maryland,* 21201, United States of America

Recent evidence has suggested that there may be significant relationships between leukemia occurring in household pets and that occurring in humans. The present analysis, conducted in collaboration with Dr. Hipolito Pabon of Colombia, is based upon the Tri-State Leukemia Survey of a decade ago. Detailed animal contact histories of a large number of leukemic children as well as controls were taken. The results are being analyzed in terms of the numbers and types of animal contacts among the leukemic children and controls during their life-times as well as during the relevant pregnancies of the mothers. All the data in this study have been processed and a master card has been prepared for the analysis of the findings.

### 71. A TIME-SPACE CLUSTERING ANALYSIS OF CHILDHOOD MALIGNANCY IN NORTH WEST ENGLAND

*Birch, J. M., Marsden, H. B., Hillier, V.,* University Hospital of South Manchester, Dept. of Epidemiology & Social Research, *W. Didsbury, Manchester M20 8LR, England, United Kingdom*

Previous studies of this type have been carried out on leukemias and some lymphomas and have produced negative results or evidence of weak clustering. The Manchester Children's Tumor Registry is population-based with almost complete ascertainment and a high degree of diagnostic accuracy. It therefore provides a unique body of data for this type of analysis. The address at the time of each child's birth is known and it is felt that in the case of childhood cancer this may be a more appropriate reference than the address at time of onset of the disease. Two Ordnance Survey grid references, accurate to within 0.1 Km, have been allocated to each case included in the Manchester Children's Tumor Registry between 1 January 1954 and 31 December 1973 corresponding to the child's place of residence at its time of birth and at the time of onset of its disease. These data are being analyzed, using the methods described by Pike and Smith, 1968, and Smith et al., 1976, to detect any space-time interaction. The data will be analyzed as a whole, by disease group and by age group.

### 72. CHILDHOOD CANCER

*Rahim, M. A., Ahmed, Q. A., Elahi, M. F., Hossain, M. A., Islam, K. M., Kabir, M. A., Khaleque, S. A., Miah, M. N., Sarma, S. K.,*

Dacca Medical College Hospital, Dept. of Radiotherapy & Chemotherapy, *49 E. Azimpur Govt. Estate, Dacca 5, Bangladesh*

Factors affecting a child suffering from malignant neoplasms will be studied under the auspices of the Bangladesh Cancer Epidemiology Research Program (BCERP). The aim of the study is (1) to determine the occurrence and age, sex and religious distribution of childhood neoplasms (primarily lymphomas and leukemias); (2) to study the geographical distribution of these diseases in different districts; (3) to calculate mortality in the light of cases registered by the BCERP and (4) to plot an area map for the study of time-space clusters. Radiotherapy, hematology and histopathology units of the radiotherapy centers in Bangladesh will participate and BCERP tumor registry forms will be utilized for recording. Subsequent compilation and analysis will be done centrally at BCERP.

### 73. CHILDHOOD CANCER IN EAST JAVA

*Hoediasmoro, D. S.*, Universitas Airlangga, Faculty of Medicine, Dept. of Pathology, *Jalan Dharmahusada No. 47, Surabaya, East Java, Indonesia*

This is a relative frequency study of childhood cancer (between 0-12 years of age) found in the Department of Pathology, Faculty of Medicine, University of Airlangga in Surabaya. Most cases in this Department are from the East Java area. Age and sex distribution and geographical variations are to be examined, and the possible correlation with socioeconomic conditions will be investigated. Special attention will be given to malignant lymphoma and retinoblastoma. Information on socioeconomic conditions will be obtained by interview.

### 74. PROSPECTIVE AND RETROSPECTIVE STUDY OF HODGKIN'S DISEASE IN RURAL POPULATION IN EAST JAVA, INDONESIA

*Mertowidjoyo, K. M., Hoediasmoro, D. S., Yuwarini, E. D., Subandiri, S., Santoso Nugrahi, B.*, Universitas Airlangga, Faculty of Medicine, Dept. of Pathology, *Jalan Dharmahusada No. 47, Surabaya, East Java, Indonesia*

Children with Hodgkin's disease in East Java, Indonesia, usually come from rural areas, located near the rice fields (paddy) and from a closed community with a low socioeconomic status. The main objectives of the present study are to identify high risk groups among the population and investigate time-space aggregation of Hodgkin's disease in the population.

### 75. PROSPECTIVE STUDY OF BURKITT'S LYMPHOMA, WEST NILE DISTRICT, UGANDA

*Olwitt, G., Williams, E. H., Geser, A.*, East African Virus Research Inst., *P.O. Box 369, Arua, Uganda*

The main objective is to study the etiological involvement of the Epstein-Barr virus (EBV) in Burkitt's lymphoma (BL). Additional objectives are to study the epidemiology of the EBV and BL in the West Nile district, and the role of hyperendemic malaria in BL causation. A cohort of 42,000 children aged 0-8 years was bled in an initial phase between 1972 and 1974. During the subsequent case detection, fourteen BL cases were diagnosed in the children who were bled. The testing of the 'pre-sera' and appropriate controls showed that viral capsid antigen antibodies to the EBV had already been elevated in the BL candidates up to four years before tumor manifestation (Nature 274, (5673) 756-761, 1978). Other EBV antibody activities (early antigen and Epstein-Barr nuclear antigen) were not elevated in the pre-BL sera and the case detection in the study cohort will continue until 1979 in order to study the mechanism of how EBV infection promotes BL development. The study of BL epidemiology has confirmed that the tumor still shows significant time-space clustering and seasonal variation, thus favoring an infectious etiology. The epidemiology of the EBV is being studied in a number of sample groups which were bled repeatedly during the years 1973-1977. The testing for EBV antibodies in the sera is now progressing at the laboratory at IARC, Lyon. The BL case detection in the West Nile district will continue through 1979. Since the testing of the 14 pre-bled BL sera in 1977, 5 new pre-bled BL cases have been detected and will be tested for anti-EBV activities in 1979. The analysis of the malaria data collected in the longitudinal survey in the West Nile has indicated that malaria parasitemia declined drastically in the West Nile between 1973 and 1977. The malaria slides are now being reexamined to ensure that this observation is true.

### 76. BURKITT'S LYMPHOMA PROJECT, MARA REGION, TANZANIA

*Brubaker, G. R., Geser, A., Kupferschmidt, H. G., Kilama, W.*, Shirati Mission Hospital, *Musoma, Tanzania*

The general objective is to study the epidemiology of Burkitt's Lymphoma (BL) and, more specifically, to investigate the role of hyper-endemic malaria in BL causation. In order to see whether hyper-endemic malaria is necessary for BL development, a malaria suppression trial is being carried out. Chloroquine tablets are distributed twice monthly to approximately 90,000 children aged 0-10 in order to reduce malaria to hypoendemic levels. The malaria suppression was initiated in 1977 and will be continued for five years, during which the incidence of BL will be carefully monitored in the area. The prevalence of malaria parasitaemia declined satisfactorily during the first year of the trial but since the end of 1978 it has returned to the previous high levels. Drastic measures are now being taken to rectify this situation. The program will continue until the end of 1982.

### 77. HODGKIN'S DISEASE IN NIGERIAN AND AMERICAN CHILDREN

*Olisa, E. G., Williams, A. O.*, University of Ibadan, *Bauchi Rd., Jos, Nigeria*

The histological classification of Hodgkin's disease in Nigerian and American children is still being studied. Materials were collected from Ibadan University Teaching Hospital and Murtala Mohammed Hospital, Jos, both in Nigeria, and a few cases were obtained from Howard University Children's Hospital in Washington, D.C., U.S.A. The American cases are 150 in number, whilst the number from Nigeria is 84. Collection continues. The natural history and histological patterns of the disease are being studied in relation to granulomatous infections, in particular tuberculosis and leprosy.

### 78. NON-HODGKIN'S LYMPHOMAS IN CHILDREN

*Schwartz, L. I., Becu, L. N., Bonessana, C. A., Sica, M. I.*, Hospital de Ninos de Buenos Aires, Dept. of Pathology, *Gallo 1330, 1425 Buenos Aires, Capital Fed., Argentina*

From 1965 to 1977 a total of 140 children with non-Hodgkin's lymphomas attended the Oncology Unit of the Children's Hospital of Buenos Aires. A male preponderance was found and the peak age was five years. The most frequent location was the abdomen, in particular the ileocaecal region. The histological pattern in a high percentage was the diffuse poorly differentiated lymphocytic form. The main objectives of future epidemiological research will be: detection of primary immunodeficiency disorders, and evaluation of the frequency of herpes and/or other virus infections.

### 79. CHILDHOOD ENVIRONMENT AND RISK OF HODGKIN'S DISEASE

*MacMahon, B., Swanson, G. M., Evans, A. S., Long, J., Gutensohn, N.*, Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts*, 02115, United States of America

The objectives of this study are (1) to evaluate the hypothesis that risk of Hodgkin's disease is a function of factors in the childhood environment which inhibit infectious transmission; in particular, family size, birth order, and social class; (2) to re-evaluate the association between tonsillectomy and Hodgkin's disease; (3) to evaluate occupational exposures and Hodgkin's disease; (4) to establish a serum bank. This is a two-part population-based case-control study. Part I is conducted in a defined population in eastern Massachusetts. A 4 1/2 year incidence case series has been identified and surviving cases interviewed at home. Age- and sex-matched controls are drawn from the general population and similarly interviewed. Siblings of cases comprise a second control group. Sera are obtained from cases and sibs. Part II is conducted in a defined population in Detroit, Michigan. A similar incidence series has been identified and information is gathered from live cases and sibling controls by mail questionnaire.

## 2. NEPHROBLASTOMA AND OTHER SOLID TUMORS

### 80. NATIONAL REGISTRATION OF CHILDREN WITH RETINOBLASTOMA IN JAPAN

*Minoda, K.*, University of Tokyo, Branch Hospital, Dept. of Ophthalmology, *3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112, Tokyo, Japan*

Retinoblastoma is the most common intraocular malignant tumor in Japan. To investigate epidemiology, genetics, pathology and clinical aspects of retinoblastoma in Japan, the national registration of retinoblastoma children in Japan was started in 1975 by the Committee for National Registration of Retinoblastoma Children, consisting of 44 ophthalmologists and three other scientists. Interim reports have appeared in Acta Soc. Opthalmol. Jpn. 80: 1648, 1976, and in the proceedings of the International Symposium on Retinoblastoma, Jpn. Opthalmol. 22, No. 3, 1978.

### 81. EPIDEMIOLOGY OF CHILDHOOD RHABDOMYOSARCOMA

*Grufferman, S., Wang, H. H.*, Duke University, School of Medicine, Dept. of Pediatrics, *Box 3711, Durham, North Carolina,* 27710, United States of America

A survey has been conducted of the entire state of North Carolina to determine the incidence of rhabdomyosarcoma in persons 0-14 years of age during 1967-1976. A threefold increase in incidence has been found during the study period. A case-control approach is being used to study the descriptive epidemiology of childhood rhabdomyosarcoma as well as associations with potential antenatal, childhood, familial and environmental etiological exposures.

### 82. OBSERVATIONS ON THE PATHOLOGY OF HODGKIN'S DISEASE AND OTHER LYMPHOMAS IN CHILDHOOD

*Erdos, Z., Romhanyi, E.*, Semmelweis Orvostudomanyi Egyetem, Dept. of Pediatrics, *Ulloi Utca 26, Budapest, Hungary*

OBJECTIVES: Investigation of Hodgkin's disease in childhood, with special attention paid to the nephrosis syndrome occuring as a complication. Furthermore, the following research is ongoing: the epidemiology of Wilms' tumor plus investigations of the optimal therapy of the above-mentioned diseases, especially with the newest medicaments.

### 83. EPIDEMIOLOGICAL ASPECTS OF JUVENILE ANGIOFIBROMA

*Rolon, P. A., De Lopez, B. H.*, Registro Nacional de Patologia Tumoral, Dept. of Pathology, *G. Arias y Tte. Rodi, Asuncion, Paraguay*

The frequency of this tumour is being investigated in a defined population in Paraguay in search of epidemiological clues.

### 84. SEROEPIDEMIOLOGICAL STUDIES ON NASOPHARYNGEAL CARCINOMA AND BURKITT'S LYMPHOMA

*Linsell, C. A.*, Centre International de Recherche sur le Cancer, *150 Cours Albert Thomas, 69372 Lyon Cedex 2, France*

SCOPE: Research activities aimed at studying the association between EBV, Burkitt's lymphoma and NPC.

Results will be helpful in defining the viral etiology of various types of human cancer and in defining approaches for this control.

The studies under this contract are being developed as three projects: 1. The prospective study in Africa (Uganda) to determine the serological status of African children in relation to EBV. 2. The epidemiology of EBV in different population groups. 3. Studies on the etiology of nasopharyngeal carcinoma.

### 85. THE PATHOLOGY AND EPIDEMIOLOGY OF GERM CELL TUMORS

*Marsden, H. B., Swindell, R., Birch, J. M.*, University Hospital of South Manchester, Dept. of Epidemiology & Social Research, *W. Didsbury, Manchester M20 8LR, England, United Kingdom*

This study was prompted by an increase in the incidence of these tumors, as assessed by the Manchester Children's Tumor Registry, which became significant in 1978. The pathology of all cases in this 25-year series, which include teratomas, yolk sac tumors and germinomas, has been reviewed to ensure diagnostic accuracy. The case-notes of each patient were carefully scrutinized for factors which may be of etiological importance and the mother's ante-natal records were also examined where these were available. These data are currently being analyzed. It is planned to extend this retrospective study to include cases in adults and a prospective case-control study of all cases aimed at the elucidation of etiological factors is also planned. Emphasis will be placed on determining the frequency of associated malformations and other tumors in the patients and their families and exposure to possible environmental carcinogens. Controls will be selected from the population and matched for age, sex and race.

### 86. GEOGRAPHICAL DISTRIBUTION OF MALIGNANT NEOPLASMS OF THE BRAIN IN CANADA

*Neutel, I. C.*, University of Ottawa, Faculty of Medicine, Dept. of Epidemiology & Community Medicine, *1145 Carling Ave., Lady Grey Bldg., Ottawa, Ontario,* K1Z 7K4, Canada

Malignant neoplasms of the brain have received very little epidemiological attention in spite of the low survival rate and their occurrence in childhood or early adulthood. A few studies dealt with their general distribution in the United States and Denmark and only one studied the geographical distribution in relation to environmental factors. This project will study the geographical distribution of brain tumours across Canada using both mortality and incidence data by calculating age-adjusted mortality and incidence rates for census divisions. These rates can be related to various environmental variables known for the census divisions. In addition, this study will investigate the occupations recorded for a selected group of brain tumour deaths and compare them with those of a matched group of controls. Of special interest will be occupations likely to involve chemical or radiation exposure. Prenatal radiation has been shown to increase the risk of childhood cancer of the central nervous system, and the same situation may apply to adult brain cancer.

### 87. ETIOLOGY OF CHILDHOOD BRAIN TUMORS

*Leviton, A., Austin, D. F., Child, M. A., Kolonel, L. N., Aschenbrenner, C., Albert, S., Key, C. R., Lyon, J. L., Weiss, N. S.*, Children's Hospital Medical Center, Dept. of Neuroepidemiology, *300 Longwood Ave., Boston, Massachusetts,* 02115, United States of America

The purpose of this case-control study is to identify risk factors for the most common subtypes of the three most common site-specific brain tumors (cerebellar gliomas, medulloblastomas and supratentorial gliomas). Cases consist of all children with these types of brain tumors identified within the catchment areas of the eight participating SEER (Surveillance, Evaluation and End Results) Registries between 1/1/78 and 12/31/81. Three controls will be obtained for each case through Random Digit Dialing and will be matched for age (3 years), sex and race. Parents of cases and controls are asked by questionnaire to provide information on the numerous exposures that might influence the risk of brain tumors in children. The null hypothesis to be tested is that each variable has the same distribution among cases and controls.

### 88. EPIDEMIOLOGIC STUDY OF CHILDHOOD GLIOMAS

*Nasca, P. C.*, State Bureau of Cancer Control, *Empire State Plaza, Tower Bldg. Rm. 565, Albany, New York,* 12237, United States of America

Our general objective is to determine, by means of an epidemiologic case-control study, the importance of various prenatal and childhood environmental exposures in the etiology of childhood gliomas. Special emphasis will be placed on prenatal and early childhood exposures to drugs, chemicals, radiation, tobacco, immunizations and animals. Selected birth characteristics including maternal age, parity and season of birth will also be examined.

Approximately 400 patients with childhood gliomas should be available for study. This sample size and a control-to-case ratio of 2:1 shall enable us to investigate the study variables with respect to the more common histologic subtypes. Demographic, pathologic and clinical data will be collected from the hospital records of each patient, utilizing a standardized form. Further data will be collected through telephone interviews

with the mothers of each patient and control. These will be validated by comparing the mothers' responses with physician and hospital records.

### 89. PEDIATRIC NEUROEPIDEMIOLOGY

*Schoenberg, B. S., Schoenberg, D. G., Mellinger, J. F., Gomez, M. R., Christine, B. W., Kudrjavcev, T.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Neurological & Communicative Dis. & Stroke, Section of Neuroepidemiology, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The project documented the frequency of primary intracranial neoplasms in the pediatric populations of Rochester, Minnesota, and the State of Connecticut. In addition, we investigated the magnitude and risk factors for cerebrovascular disease in infants and children in the Rochester, Minnesota, population. We have also initiated a study of the temporal trends in the incidence of cerebral palsy.

BIBLIOGRAPHIC REFERENCES: Schoenberg, B.S.: Risk Factors for Stroke in Infants and Children. In Goldstein, M., Bolis, L., Fieschi, C., Gorini, S., and Millikan, C.H. (Eds.): Cerebrovascular Disorders and Stroke. New York, Raven Press, 1979, pp. 313-324.

### 90. EPIDEMIOLOGY OF INTRACRANIAL NEOPLASMS

*Preston Martin, S., Henderson, B. E., Gardner, M. B., Mack, T. M.*, University of Southern California, School of Medicine, Dept. of Pathology, *2025 Zonal Ave., Los Angeles, California*, 90033, United States of America

A large case-control study of two subgroups of patients with primary intracranial neoplasms is to be performed in Los Angeles County: intracranial tumors of all histological types first occurring in children and young people under age 25 from 1972 to 1977; and incident intracranial meningiomas in men from 1972 to 1975. The study has been designed to test the hypothesis that previous radiation exposure is causally related to the development of these tumors, to test previously suggested causal associations, to discover new associations and to delineate the characteristics of the high risk groups. Cases with specified intracranial tumours will be identified by the Los Angeles County-University of Southern California Cancer Surveillance Program. Questionnaires have been designed to obtain data on radiation exposure, occupation, consumption of tobacco and drugs, medical history, and family history of tumors. Standard matched pair analyses of multiple variables will be performed.

## E. OTHER ENVIRONMENTAL AND ETIOLOGIC FACTORS AND THE INCIDENCE OF CHILDHOOD CANCER

### 91. TUMORS OF CHILDHOOD IN EGYPTIAN CHILDREN - EPIDEMIOLOGICAL AND STATISTICAL STUDIES

*Boutros, S. G.*, Cancer Registry of the Metropolitan Cairo Area, Inst. of Statistical Studies and Research, *Tharwat St., P.O.B. 1017, c/o Cairo University, Dokki, Cairo, Egypt*

OBJECTIVE: Assess statistically as far as possible the magnitude of childhood cancer in Egyptians below the age of 20.

APPROACH: (a) 670 cancer cases below the age of 20, reported to the Cancer Registry for the Metropolitan Cairo area during the period 1973-1975, were studied. (b) Reported deaths among those under 20 years of age in the period 1933-1972 were analyzed.

PROGRESS AND RESULTS: a. Cancer in the age period 0-19 constituted 7.94% of the total cancer in all age groups, with male preponderance, M:F ratio 1.8. b. The five most prevalent tumor sites in childhood are: malignant tumors of lymph nodes (29.1%); malignant tumors of bone and joints (20.0%); hematopoietic and reticuloendothelial system (12.8%); malignant tumors of the eye and the central nervous system (11.3%); and malignant tumors of connective and soft tissue (6.0%). c. The order of the frequency of histological typing is as follows: lympho-hematopoietic tissue ranks first (36.72%), followed by sarcoma (33.13%), carcinoma (13.17%) and nervous tissue tumors (9.85%). d. Childhood cancer death rate rose from 0.17 per 100,000 population in 1930 to 3.37 in 1970.

The main concern of the study is some of the most common forms of cancer in Egyptian children, such as Hodgkin's disease, malignant tumors of the bones, leukemias, and tumors of the central nervous system.

### 92. EPIDEMIOLOGY OF CHILDHOOD MALIGNANCIES IN JAPAN

*Hirayama, T.*, Ministry of Health & Welfare, Epidemiology Div., *Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Tokyo, Japan*

Patterns of occurrence of childhood malignancies in Japan are being studied in relation to selected risk factors based on data from nationwide registration. A total of 10,575 children (5,951 males; 4,624 females) under age 15 were registered between 1969 and 1977. Malignancies included leukemia (4,607), malignant lymphoma (750), neuroblastoma (1,002), Wilms' tumor (485), liver tumor (230), retinoblastoma (892). Age-specific incidence rates were calculated for each. When compared with vital statistics figures for all Japan, maternal ages had little or no influence, but significant risk elevation was noted under age three with increase in weight at birth, for leukemia, neuroblastoma, Wilms' tumor, testis tumor, and teratoma. Abdominal radiation exposure during the later part of pregnancy was noted to enhance leukemia risk in those children when compared with 1,011 controls of similar age. Down's syndrome was frequent in leukemia cases under age three and many cases of congenital malformation, including seven cases of hemihypertrophy, five of aniridia, six of congenital heart disease, were recorded co-existent with Wilms' tumor. The mean ages for retinoblastoma were five, six and seventeen months for bilateral, unilateral with family history, and unilateral without family history cases respectively. Analysis continues.

### 93. EPIDEMIOLOGY OF CHILDHOOD CANCER IN THE PROVINCE OF TORINO, ITALY

*Pastore, G., Anglesio, E., Terracini, B.*, Universita degli Studi di Torino, Clinica Pediatrica, Serv. di Oncologia, *Piazza Polonia 94, c/o Ospedale Regina Margharita, 10126 Turin, Italy*

A special childhood cancer registry (children aged 0-14) for residents in the province of Torino (total population at the time of the 1971 census: 2,287,016, of whom 497,223 were aged 0-14) has been operating since 1965. Cases are recorded according to ICD and histological types. Data for the 1967-74 period have been published (Rivista Italiana di Pediatria 5: 337-345, 1979). The collection of cases and their analysis have been completed for the period 1975-78. Incidence rates are similar to those of other industrialized countries in the Western World. Incidence rates have been calculated for residents in the city of Torino and residents in the rest of the province as well as for different areas within the province. The incidence rate for all cancers and for neurogenic tumors was higher in the city of Torino than in the rest of the province in the period 1967-74, but not between 1975 and 1978. By 1982 collection of cases will be completed for the period up to December 1981. Trends in incidence, mortality and lethality are being investigated, as well as the distribution of cancer in children among the indigenous population as compared to the population immigrating from other parts of Italy.

### 94. EPIDEMIOLOGY OF CHILDHOOD TUMORS

*Shah, P. M., Patel, O. D., Gawadia, M. L., Shah, A. K.*, Gujarat Cancer & Research Inst., Chemotherapy & Medical Unit, *New Civil Hosp. Campus, Ahmedabad 380016, Gujarat State, India*

The aim of this study is to determine the pattern of childhood cancer in Gujarat State. With the effective control of infectious diseases in childhood, malignant disorders in childhood have become an important cause of mortality in pediatric practice. About 150 new cases of pediatric tumors are registered every year at the Gujarat Cancer Research Institute.

### 95. STUDIES ON THE ETIOLOGY OF CHILDHOOD TUMORS

*Marsden, H. B., Jones, P. H., Birch, J. M.*, University Hospital of South Manchester, Dept. of Epidemiology & Social Research, *W. Didsbury, Manchester M20 8LR, England, United Kingdom*

This is a population-based study on the incidence of childhood malignancy. Details of all cases of malignancy occurring in the child (0-14 years) population (approximately 1 million) in the North West Regional Health Authority have been collected

since 1954. Clinical records and microscopic slides are retained for study. Time-space clustering analysis is being carried out. Factors which may be of etiological significance in childhood malignancy, with emphasis on genetic and environmental aspects, including drugs in pregnancy and parental occupation, are being investigated. A detailed study of family histories is being made with particular emphasis on congenital malformations and malignancies in family members. The quality of life in long-term survivors is being assessed.

### 96. TUMORS IN CHILDREN - SEX- AND AGE-SPECIFIC INCIDENCE RATES IN RELATION TO HISTOGENESIS

*Powell, J., Waterhouse, J. A.,* Regional Cancer Registry, *c/o Queen Elizabeth Med. Ctr., Birmingham B15 2TH, England, United Kingdom*

Tumors in children differ sharply from those of the adult, particularly in the systems of the body in which they most commonly occur. Examination of sex- and age-specific incidence rates (for single years from birth) indicates the well-known marked variations during the first decade of life, although from age ten onwards the difference between childhood and adult cancer becomes one of quantity rather than quality. A method of classification according to histogenesis has been developed and, since the data are from a population-based registry, variation in the age at onset appears to provide a useful model for studying the relationship between the different types of malignancy and possible aetiological factors, the organs affected depending in some types on the gestational age of exposure.

### 97. ANALYSIS OF DATA FROM THE OXFORD SURVEY OF CHILDHOOD CANCERS

*Stewart, A. M., Draper, G. J., Kinnier Wilson, L. M., Kneale, G. W.,* University of Birmingham, Dept. of Social Medicine, Regional Cancer Registry, c/o Queen Elizabeth Med. Ctr., *P.O. Box 363, Birmingham B15 2TH, England, United Kingdom*

Factors affecting the probability of a child dying from a malignant disease within 14 years of birth are being studied.

### 98. HEREDITY AND ENVIRONMENT IN CHILDHOOD CANCER

*Meadows, A. T., Knudson, A. G., Kramer, S., Obringer, A., Hopson, R.,* Children's Hospital of Philadelphia, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania,* 19104, United States of America

Although cancer is the leading cause of morbidity and mortality in children beyond infancy, etiologic factors are not known, except in few cases. Clues from epidemiologic studies in adults and from animal data suggest that substances which could produce germinal mutations may also act to produce malignant transformation in somatic cells.

We propose to investigate possible etiologic factors in childhood cancer, which could explain the uniform incidences of some cancers around the world (spontaneous fraction), the preponderance of multicentric or bilateral cases in some instances (germinal mutations), and the environmental factors causing both somatic and germinal mutations. By identifying individuals at high risk of childhood cancer we may be able to devise methods of prevention.

The methods used will involve: (1) The Greater Delaware Valley Pediatric Tumor Registry (GDVPTR), a population based registry, in order to monitor the incidence of childhood cancer in a 31-county region and to determine tumor-specific incidence rates especially comparing the incidence of multicentric cases with expectations. (2) A case-control study to test hypotheses concerning important risk factors in the etiology of childhood cancer. This would include approximately 650 children with various malignant diseases and 1300 controls to investigate pre-natal, gestational, and post-natal exposures such as those known to be mutagens or carcinogens in animal systems and adults.

### 99. OHIO CENTRAL DATA BASE FOR CHILDHOOD CANCER

*Newton, W. A., Dyment, P. G., Kastelic, J., Stout, R. A., Robinson, M., Gross, S., Lampkin, B.,* Ohio State University, Columbus Campus, Children's Hospital, *561 S. 17th St., Livingston Pike, Columbus, Ohio,* 43205, United States of America

The objective is to provide baseline information on demographic patterns for cancer morbidity and mortality in Ohio children. This includes case-finding information regarding type of cancer by age, race, sex, place of residence, staging at initial diagnosis and institution of initial diagnosis. Abstracts are being prepared on hospital discharge of all newly diagnosed children with cancer beginning January 1975 from all the major treatment centers for children in Ohio. These abstracts utilize forms currently in use in a broader data collection program, the Children's Hospital Automated Medical Program (CHAMP), a medical research computer center located in Children's Hospital, Columbus, Ohio. In addition, an epidemiological questionnaire to be completed by parents is also being collected. This includes general questions on family history, including cancer in relatives and malformations, with additional specific information on patients with leukemia, brain tumors, Wilms' tumor and malignant lymphoma.

### 100. SURVEILLANCE OF CHILDHOOD NEOPLASMS IN HARRIS COUNTY, TEXAS

*Fernbach, D. J., Starling, K. A., Steuber, C. P., Shepherd, D. A.,* Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

This population-based registry of cancer in children aims to evaluate occurrence, determine geographical variations, and evaluate annual variations in incidence for specific tumors by census tract, ethnic groups, etc.

### 101. DATA BANK FOR STUDY OF THE EPIDEMIOLOGY OF CHILDHOOD CANCER

*Grufferman, S., Falletta, J. M., Wang, H. H., Kimm, Y. S.,* Duke University, School of Medicine, Comprehensive Cancer Center, *Box 3711, Durham, North Carolina,* 27710, United States of America

The major objective of this study is to learn more about the epidemiology of childhood cancers. A questionnaire will be administered to the parents of all childhood cancer patients seen at the Duke Medical Center and to matched hospital controls with information banked for later case-control studies. The epidemiologic data collected will be used to study the descriptive epidemiology of various childhood tumors (singly and in various groupings) as well as associations with potential antenatal, childhood, familial, and environmental etiologic exposures. Information modules on nutrition and radiographic findings are to be added in the near future.

### 102. NATIONAL PEDIATRIC REGISTRY (POPULATION-BASED)

*Ford, J. M., Bishop, K., Campbell, P., Lay, H., McWhirter, W., Newman, N., O'Gorman Hughes, D., Rice, M.,* Health Commission of New South Wales, Central Cancer Registry, *P.O. Box K110, Haymarket, Sydney, N.S.W. 2000, Australia*

The National Pediatric Registry was established by the Pediatric Group of the Clinical Oncological Society of Australia (of the Australian Cancer Society) in 1976, to collect and collate incidence data from January 1977, for all pediatric cancers (0 to 14 years) for all States in Australia. This is the first national collection of cancer incidence statistics. Notification of cases is voluntary, and is supervised in each State by a co-ordinator who is a member of the Pediatric Group of the Clinical Oncology Society of Australia. The notifications are forwarded to the Central Co-ordinator, who is the Registrar of the New South Wales Central Cancer Registry. The data are processed parallel with the New South Wales cancer data and a separate file is maintained. Cancer incidence by site, age, sex, cell type, country of birth of the child and his parents and grandparents, racial origin, and geographical location of the patient is currently being analyzed. The first of a series of reports is to be published in 1980.

### 103. CHILDHOOD CANCER REGISTRY

*Draper, G. J., Kinnier Wilson, L. M., Lennox, E. L.,* University of Oxford, Dept. of the Regius Professor of Medicine, *S. Parks Rd., Oxford OX2 6HE, England, United Kingdom*

A registry for childhood neoplasms occurring in England, Scotland and Wales has been established with the following objectives: (1) To obtain estimates of incidence, mortality and

survival rates, (2) to provide a basis for epidemiological, genetic and medical care studies, (3) to provide a service to other research workers. Registrations of cancer in children below age 15 and deaths below age 16 are reported to the Childhood Cancer Research Group by the Office of Population Censuses and Surveys, the Information Services Division of the Scottish Health Service, regional cancer registries, and clinicians. This is supplemented by clinical information derived from hospitals and general practitioner records. A classification system particularly appropriate for childhood cancer and based on the International Classification of Diseases for Oncology has been developed. Comprehensive data on incidence, mortality and survival have been analyzed and will be published by the Office of Population Censuses and Surveys. Studies currently in progress include: (1) Comparisons of survival rates for children with leukemia and Wilms' tumor included in MRC clinical trials with those for children not included, (2) the provision of treatment for children with cancer, (3) studies to determine whether there is an increased incidence of cancer in the parents of children with cancer.

### 104. CHILDREN'S CANCER REGISTRATION

*Hanawa, Y.*, Kanagawa Children's Medical Center, *3-138-4 Mutsukawa, Minami-ku, Yokohama 232, Japan*

The object is to establish registration of childhood cancer on a national basis in Japan.

### 105. CHILDHOOD CANCER IN ALBERTA

*Birdsell, J. M., Morgan, K.*, Southern Alberta Cancer Centre, Dept. of Epidemiology, *2104 2nd St. S.W., Calgary, Alberta,* T2S 1S5, Canada

Files of children diagnosed with cancer and registered with the Alberta Cancer Registry during the past 10 years are being reviewed. In addition to descriptive statistics on incidence and mortality by age, sex, site, and histology, this study will provide information on survival rates. Variables which might provide leads to etiological factors include occupation of father, place of birth and/or residence, reproductive history of mother, presence of congenital malformations, and family history of cancer. The total number of childhood cancer cases diagnosed in Alberta for the period 1968-1977 was 543 (0-14 years of age), 298 males and 245 females. The incidence of childhood cancer in Alberta has been compared with that of other population-based registries in Manitoba, Saskatchewan, Norway, and Birmingham, UK, and with results of the US Third National Cancer Survey. However, the incidence of leukemia in Alberta male children appears to be lower than the average. Data from detailed review of files for the three-year diagnosis period, 1975-77, are being analyzed in order to assess the quality of information available. Additional information will be obtained from vital statistics registrations in the province.

### 106. CHILDHOOD CANCER AND PARENTS' OCCUPATION

*Hemminki, K. J., Partanen, T. J., Salonen, T.*, Inst. of Occupational Health, Dept. of Industrial Hygiene & Toxicology, *Haartmaninkatu 1, SF00290 Helsinki 29, Finland*

The study aims to find out whether any correlation exists between the occupational activities of parents and cancer in their children. The material consists of cancer cases in children under 15 years of age recorded by the Finnish Cancer Registry in the period 1959-1968. The parents' occupations were traced from the records of the antenatal clinics. Controls were matched for age and place of birth. The material is being analysed with regard to the occupation of the parents.

### 107. ASSOCIATION OF PARENTAL OCCUPATION WITH CHILDHOOD CANCER CASES - NCI

*Spirtas, R.*, U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

Current studies of the association between industrial agents and reproductive effects have focused on health outcomes prior to and including delivery. For those pregnancies resulting in 'normal' live births, it is possible that later (after one year) adverse effects such as neoplasms could be directly associated with exposures from agents identified in the occupational/industrial groups of the mother and/or father of a child.

The purpose of this proposed project is to survey childhood cancer cases in an attempt to provide an overview of associations between certain malignant neoplasms and parental occupational/industrial groups and to suggest studies of specific occupational/industrial groups that indicate excess cancer risk for workers' offspring.

The work on the project would be carried out under contract. The contractor would abstract, code, and analyze a data set of childhood cancer cases to accomplish the define purposes of the project.

FY 79 ACCOMPLISHMENTS: An interagency agreement between the Food and Drug Administration and NIOSH was completed.

### 108. THE ONCOGENIC POTENTIAL OF CYTOMEGALOVIRUS PERSISTENT IN LYMPHOID CELLS

*Joncas, J. H.*, St. Justine Hospital, Dept. of Immunovirology, *3175 St. Catherine Rd., Montreal, Quebec,* H3T 1C5, Canada

OBJECTIVE: To characterize and determine the oncogenic potential of a CMV strain persisting in the urine and in the lymphoblastoid cell lines established from the peripheral blood of an infant with congential CMV infection.

APPROACH AND PROCESS REPORT: We have been able to detect by molecular hybridization an unexpressed cytomegalovirus genome in 2 of 3 tested, out of 5, available lymphoblastoid cell lines of the B cell type obtained successively, from age 3 to 36 months, from an infant with proven cogenital cytomegalovirus infection. Additional cord blood cell lines obtained by cocultivation of one of the CMV genome positive cell lines with cord blood lymphocytes, thymus or bone marrow cells were also found to be CMV genome positive by molecular hybridization. All the cell lines whether CMV genome positive or not, are also positive for the Epstein-Barr virus (EBV) genome. The lines positive for CMV in contrast to the line positive only for the EBV genome spontaneously express EBV-early antigen (EA) and synthesize large amounts of immunoglobulin M. The CMV strain isolated from the baby's urine has been characterized by analysis of the electrophoretic pattern of the restriction enzymes digestion fragments of its DNA and by reciprocal hybridization with the DNA of other CMV strains: it has been found to be very similar but not identical with the AD-169 strain of CMV. We have also carried out two unsuccessful attempts so far to transform cord blood leukocytes with this particular strain of CMV. Experiments to date to determine any antibody specificity of the IgM detected in the CMV genome positive lines, gave negative results. These experiments included tests to obtain rosettes of the cells with sheep or horse red blood cells (heterophil agglutinins) with fetal red blood cells ( anti i-antibodies). Further experiments include study by immunofluorescence and molecular hybridization of the cell clones currently obtained, the detection of at least a membrane antigen detectable by sensitized lymphocytes similar to Lydma in the EBV system using autologous lymphocytes from the infant himself, now 4 years of age, additional attempts to detect intracellular or cell surface CMV antigens using additional CMV-positive, EBV-negative sera (4 such different sera have already been tested without positive results). (Text Abridged.)

### 109. HERPES VIRUSES IN CHILDHOOD CANCER

*Stematsky, G. T., Zaizov, R., Kriss, S., Sayar, Y.*, Ministry of Health, Central Virus Lab., *P.O. Box 8255, Tel Aviv, Israel*

Groups of children with various tumor types are being tested by the indirect immunofluorescence test for the presence of antibodies to Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes type 1 and 2 and varicella-zoster (VZ) viruses in order to obtain information on primary infections and on frequency of reactivation or reinfection with these viruses in sick as well as healthy children. Correlation analysis of serological profile with age, sex, ethnic origin and clinical data will be carried out.

### 110. THE OXFORD PREGNANCY STUDY

*Wald, N. J.*, University of Oxford, Radcliffe Infirmary, Cancer Epidemiology & Clinical Trials Unit, *Oxford OX2 6HE, England, United Kingdom*

This study is an investigation into the feasibility of linking antenatal serum samples to subsequent childhood cancer with a view to investigating the role of, for example, virus infection in the development of childhood cancer. Data have also been used to investigate the relationship between maternal serum alpha-fetoprotein levels and fetal neural-tube defects, spontaneous abortion, multiple pregnancy, diabetes mellitus and low birth weight. At present about 20,000 women have been recruited into the study. Children born to women in the study are identified and their National Health Service records tagged in Southport, so that in the event of cancer or death a notification will be sent to Oxford. At least one other center in Europe is performing a similar study, and with the collaboration of the International Agency for Research on Cancer the progress of different studies is periodically reviewed.

### 111. LIVER TUMORS IN CHILDREN AND ADULTS

*Pollice, L. M., Resta, L., Giardina, E. D., Dammacco, F.*, Universita degli Studi di Bari, Fac. di Medicina, Institute of Pathological Anatomy, *70124 Bari, Italy*

Following a study on primary hepatic tumors in infancy and childhood, a general study on hepatic tumors is under way. Correlations between viral hepatitis and hepatocarcinoma are investigated.

### 112. HEALTH EFFECTS IN CHILDREN EXPOSED TO VINYL CHLORIDE

*Ziskind, R. A., Wilkinson, G. S.*, Science Applications Inc., Energy Environment Systems Division, *1801 Ave. of the Stars, Suite 1205, Los Angeles, California,* 90067, United States of America

Although a considerable body of occupational and laboratory toxicological data have demonstrated the carcinogenic action of vinyl chloride monomer (VCM), there appears to be little epidemiological information regarding health effects in children exposed to ambient levels of VCM. A pilot study consisting of a cohort of elementary school children who attended a school situated in close proximity to a PVC manufacturing plant will be conducted for potential health effects 10 to 20 years after exposure. Students will be grouped into three graduated exposure categories based upon estimates of total VCM concentrations received. Plant production history will be linked with pupil records, air monitoring data and dispersion calculations to subgroup the cohort. A number of mortality and morbidity indicators and data bases will be examined in order to contrast all exposure groups with zero exposure population.

### 113. EPIDEMIOLOGY

*George, S. L.*, St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

## II. PRECLINICAL CHEMOTHERAPY STUDIES IN MODEL SYSTEMS OF PEDIATRIC NEOPLASMS

### 114. MEMBRANE BIOCHEMISTRY IN DRUG RESISTANT NEUROBLASTOMA

*Baskin, F., Rosenberg, R. N.*, University of Texas, Health Science Center at Dallas, Southwestern Medical School, Dept. of Neurology, *5323 Harry Hines Blvd., Dallas, Texas,* 75230, United States of America

Disseminated neuroblastoma, a common form of childhood cancer, has been treated with a variety of chemotherapeutic drugs. Drug induced remissions are frequently noted, but the tumor generally returns, resistant to the drugs used. As the drug resistance mechanisms were unknown for this tumor, we used the genetically homogenous C46 clone of the spontaneous murine neuroblastoma C-1300 in monolayer cell culture, to isolate and biochemically characterize variants resistant to a series of antifolates, nucleoside analogues, anthracyclines and microtubule disrupters. Resistance mechanisms, involving alterations in drug uptake and retention, or the activities of affected enzymes, proved to be neuroblastoma-specific. In demonstrating the parallel resistance of these clones in their syngeneic host, the Ajax mouse, alterations in tumorigenicity were noted suggesting changes in cell surface glycoproteins. This and collateral sensitivity to several inhibitors of glycosylation led us to examine the resistant cell's surface glycoproteins and glycolipids using whole cell surface radiolabeling techniques and fractionation by 2-dimensional gel electrophoresis and lectin-chromatography. One maytansine resistant mutant, as is typical of membrane mediated resistant cells, was cross-resistant to a wide range of lipophilic drugs, and unable to take up colchicine despite a normal content of cytoplasmic tubulin, proved to be 98% deficient in a cell surface glycoprotein, MW 90,000, pI - 5.95. We propose the examination of other drug-selected mutants, cross-resistant to maytansine, and a drug-sensitive revertant, for glycoprotein alterations, to establish causality, and to determine whether this and similarly altered glycoproteins on our other mutants represent a transcriptional, translational, post-translational or membrane assembled effect. Mindful of species variation seen in other drug resistance mechanisms, we propose to contrast this mechanism with that of diploid human neuroblastoma SK-SY-5Y maytansine resistant clones and to study the effect of the membrane glycosylation inhibitor, tunicamycin, on this drug resistance and altered tumorigenesis in an effort to understand and improve the chemotherapy of this tumor.

### 115. BIOCHEMICAL EVENTS IN DIFFERENTIATING NEUROBLASTOMA

*Rosenberg, R. N.*, University of Texas, Health Science Center at Dallas, Southwestern Medical School, Dept. of Neurology, *5323 Harry Hines Blvd., Dallas, Texas,* 75230, United States of America

Neuroblastoma, a common solid tumor of children, has been treated with limited success with cytotoxic chemotherapeutic drugs. It may spontaneously differentiate in vivo, perhaps preventing tumours from presenting themselves. In model studies, clonal mouse neuroblastoma cells grown in tissue culture with dibutyryl cAMP or other agents increasing intracellular cAMP levels are not only biochemically and morphologically differentiated but are less tumorigenic in the syngeneic Ajax mouse. We propose to investigate the correlation between differentiation, as evidenced by increases in the levels of specific markers including cAMP binding proteins, and their in vivo tumorigenicity. The transcriptional, translational and post-translational mechanisms will be studied including the effectors of transcriptional control, the nuclear acidic proteins and the changes in the synthesis and processing of m-RNAs. Control at the translational level will be studied by the analysis of levels of the in vivo synthesis of specific proteins, separated by two-dimensional gel electrophoresis, and extended by analysis of the levels of cytoplasmic messenger RNAs assayed in in vitro protein synthesizing systems. We will also investigate the altered synthesis and/or glycosylation of membrane proteins as the direct modulators of tumorigenicity. Specific alterations which correlate with reduced tumorigenicity will define a system in which to predict and test new non-toxic drugs capable of differentiating neuroblastoma in vivo.

BIBLIOGRAPHIC REFERENCES: Increase in cAMP binding protein in the transcriptionally active regions of chromatin of dibutyryl cAMP treated neuroblastoma cells. Prashad, N., Rosenberg, R.N., Ulrich, C. and Sparkman, D. (1979) FASEB Abstract, in press. Differences in the poly(A) size distribution of individual neuroblastoma messenger RNAs. Morrison, M.R., Brodeur, R., Rosenberg, R.N. and Pardue, S. (1979) FASEB Abstract, in press.

### 116. IN VITRO STUDIES ON HUMAN NEUROBLASTOMA CELLS

*Rupniak, H. T., Hill, B. T., Pritchard, J., Rein, G.*, Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Neuroblastoma is the third most common malignancy affecting children. In spite of the application of combination chemotherapy to this childhood cancer, the survival rate of children with disseminated disease has shown little improvement. An interesting aspect of this particular cancer is its rather high rate of spontaneous differentiation to benign ganglioneuroma in

the absence of treatment. Differentiation has also been noted to occur in tumors in children following chemotherapy.

We have recently established, from a patient with neuroblastoma, a cell line that consists of a mixed population of both undifferentiated and relatively differentiated cells. Current efforts are aimed at separating and characterizing these subpopulations. In culture, this cell line can be induced to undergo morphological differentiation by dibutyrylcyclic-AMP but not by a range of other agents which can nevertheless induce differentiation of mouse neuroblastoma cells. Further work is in progress to determine whether this process is complemented by biochemical differentiation in terms of catecholamine production.

### 117. COMBINED EFFECTS OF RADIATION AND CYTOTOXIC DRUGS ON THE RADIATION TOLERANCE OF THE CENTRAL NERVOUS SYSTEM

*Hopewell, J. W., Karbal, A.,* University of Oxford, Churchill Hospital Research Inst., *Oxford OX3 7LJ, England, United Kingdom*

OBJECTIVE: Chemotherapeutic agents, in particular methotrexate, are currently being used in conjunction with brain irradiation as part of the prophylactic treatment of children with leukemia. It is proposed to examine the possible effects of various drug combinations on the radiation tolerance of the central nervous system.

APPROACH: It is proposed to investigate the mechanisms responsible for the development of damage in the brain and spinal cord in experimental animals. Effects will be evaluated by the quantitative assessment of cellular changes in histological material obtained by the serial killing of treated animals. The importance of field size will be investigated.

Modifications in normal tissue and tolerance produced by radiation of the spinal cord in combination with various dose levels of intrathecal methotrexate and other drugs will be determined by establishing the proportion of animals developing paralysis after 6 months. Iso-effect doses will be compared to determine the relative changes in cord tolerance.

In the brain, radiation depletion of the cells in the subependymal plate region will be used as a measure of radiation effects. Modifications in this response, produced by drug combinations, will be evaluated.

### 118. STUDY OF METHOTREXATE POLYGLUTAMATES IN CULTURED CELLS AND IN MAN

*Whitehead, V. M., Rosenblatt, D.,* Montreal Children's Hospital, Dept. of Hematology, *2300 Tupper St., Zone 25, Montreal, Quebec, Canada*

OBJECTIVE: The aims of this research are to define conditions affecting metabolism of methotrexate (MTX) to MTX polyglutamates in a number of cell systems and to correlate this metabolism with the cytotoxic action of MTX.

APPROACH: We are studying normal human fibroblasts in monolayer culture; mammalian cell lines which metabolize MTX without increasing total cell MTX; and human blood and bone marrow cells from children with leukemia in remission and in relapse. Cells are incubated with (3H)MTX in vitro. Cells are then washed and extracts prepared and MTX and metabolites separated using Sephadex G15 gel chromatography. In the past year we have been studying the following: 1) the ability of human leukemic and normal blood cells to metabolize MTX; 2) the competition between reduced folates and MTX; 3) the long-term uptake of MTX and the loss of MTX and metabolites from pre-loaded cells with time; and 4) the distribution of MTX and metabolites in cells.

PROGRESS: We have shown that human blood and bone marrow cells and leukemic cells from children with lymphoblastic and myeloblastic leukemia accumulate MTX and metabolize it to MTX polyglutamates of progressively longer chain length in a time- and dose-dependent fashion. Thus, MTX treatment of children with leukemia is associated with accumulation of MTX polyglutamates in bone marrow and leukemic cells.

Both 5-formyltetrahydrofolate (folinic acid, citrovorum factor) and 5-methyltetrahydrofolate block accumulation of MTX and synthesis of MTX polyglutamates in human fibroblasts. This effect requires mixing of reduced folate and MTX in a ratio of 10:1.

Folinic acid has very little effect on reversing MTX-induced dU suppression in human fibroblasts when added after MTX. Co-incubation of cells with MTX and folinic acid provides some protection against MTX-induced dU suppression. We believe that folinic acid does not 'rescue' by providing a pool of reduced folate, but more likely by interfering with MTX accumulation and metabolism in cells.

We have obtained preliminary evidence that the level of dihydrofolate reductase in cells is far less than that predicted if all non-exchangeable MTX and metabolites in cells are bound to that enzyme.

### 119. DIFFERENTIATION OF MALIGNANT COLONY-FORMING CELLS FROM NON-COLONY-FORMING CELLS IN PROGRESSIVE LYMPHOID MALIGNANCIES

*Smith, S. D.,* University of Kansas, Medical Center, School of Medicine, Dept. of Pharmacology/Pediatrics, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

In this laboratory, we have identified three sub-populations of malignant lymphoid cells (MLC) that exist in the bone marrow of children with acute lymphoblastic leukemia and non-Hodgkin's lymphoma. One type is the malignant lymphoid colony-forming cell (ML-CFC) which has been successfully grown and passed in an agar assay system. This cell has an unlimited growth potential and accounts for 0.3-0.001 percent of the total tumor cells burden. A second type is a MLC with a long in vitro survival (MLC-L) which 1) will not form a colony, 2) will survive in vitro for three to six weeks and 3) accounts for up to 20 percent of the tumor cell burden in late stage disease. The third type, a MLC with a short in vitro survival (MLC-S) is a cell that dies by day 18 of the culture but is important for it comprises more than 80 percent of the total tumor cells. Recently some drug sensitivity patterns (in vitro) of the ML-CFC have been defined. These drug patterns may correspond to the patient's in vivo drug response, for such a correlation has been established for animal tumors. These exciting results encourage us to attempt to determine similar drug sensitivity patterns for non-colony-forming cells, since the ML-CFCs account for less than one percent of the total tumor cell burden. Thus any chemotherapeutic regime that is expected to be clinically significant must also kill then non-colony-forming cells (99% of the total tumor cell burden). Studies on individual patients with sequential relapses have shown that the ratio of the ML-CFC to the total tumor cell burden increases as the malignant lymphoid disease progresses. These studies show much promise but need to be expanded for an understanding of the relationship between the sub-types of malignant lymphoid cells, as well as their drug sensitivities, could provide the means to cure a child who has suffered a relapse.

### 120. THE CHEMOTHERAPY IN MICE OF HUMAN CHILDHOOD RHABDOMYOSARCOMA

*Houghton, P. J.,* St. Jude Children's Research Hospital, Dept. of Biochemical & Clinical Pharmacology, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

The aim of this study is to establish a model of human childhood rhabdomyosarcoma (predominantly embryonal) by growing surgical specimens from previously untreated patients in immune-deprived mice. These xenografts will be characterized using histologic and biochemical criteria. In each of six xenograft lines, from individual patients, the cell proliferation kinetics and chemosensitivity to a spectrum of cytotoxic agents will be studied. Resistance to agents used in current therapeutic protocols for childhood rhabdomyosarcoma will be induced in initially sensitive lines. These resistant xenografts will be used to select agents which may be used in clinically refractory disease, to study the mechanisms of resistance, to elucidate methods of retarding or preventing the onset of resistance, and to develop methods of circumventing the resistance mechanisms.

### 121. A STUDY OF THE COLONY-FORMING ABILITY OF HUMAN TUMOR CELLS OBTAINED FROM CLINICAL BIOPSIES

*Rupniak, H. T., Hill, B. T., Pritchard, J., Nicholls, J., Laskiewicz, B., Shaw, H. J., Williams, G.,* Imperial Cancer Research Fund, Cellular Chemotherapy Laboratory, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A cloning assay has recently been described that shows considerable promise as a means of predicting the clinical sensitivity of a patient's tumor by prior screening of that patient's tumor cells against a range of anti-cancer agents in vitro (Salmon et al., New England Journal of Medicine, 1978, 298, 1213).

An ongoing assessment is being made of the feasibility of extending the application of a cloning assay (developed by Courtenay et al., British Journal of Cancer, 1978, 38, 77) to a number of other malignancies. Particular emphasis is being placed on colo-rectal, head and neck, bladder and childhood tumors in collaboration with several hospital units.

By virtue of this ability of tumor cells to clone selectively in soft agar, this procedure also holds promise as a means of establishing human tumor cell lines for in vitro chemosensitivity testing.

# III. CLINICAL DIAGNOSIS AND PROGNOSIS OF PEDIATRIC NEOPLASMS

## A. DIAGNOSIS OF CHILDHOOD CANCER

### 122. EARLY DETECTION AND MONITORING OF LEUKEMIA AND TUMORS IN CHILDREN AND ADULTS

*Muller, H., Stalder, G.,* University Children's Hospital, Dept. of Genetics, *Romergasse 8, CH4005 Basel, Switzerland*

OBJECTIVES: 1) Recording of preleukemic states, i.e., hematological disorders highly conducive to leukemia. 2) Early detection of malignant lymphoma in children and adults. 3) Recording of mutagenic effects of the cytostatic therapy. 4) Cytogenetic characterization of solid tumor cells.

APPROACH: Chromosomally abnormal cells - suspected to be malignant - are to be detected and recorded by a systematic cytogenetic analysis of the tissue in question. For the chromosome analysis new staining techniques are used. Great effort is being made to investigate the cell population within a tumor supposed to be the subject of malignant transformation by using adequate techniques of cell isolation and cell culture. With relevant cytogenetic techniques defects of DNA repair mechanisms in aplastic anemia are visualized. For this purpose the cultured cells of the patient are exposed to specific aberration-inducing chemicals. After successful tumor therapy, chromosome defects and aberrations in the DNA content of sperms and somatic cells are being searched for.

PROGRESS: Every year some 150-200 new patients belonging to one of the above mentioned groups can be included in the study. The findings obtained contributed to the understanding of the significance of the chromosomal aberrations in the neoplastic process. A moderate but constantly increased frequency of spontaneous sister chromatid exchanges, indicating alterations on the DNA level, was found in a group of young patients suffering from aplastic anemia. DNA repair defects were primarily found in patients with anemia of the Fanconi type. As a rule the successful cytostatic treatment induced no persisting mutations on the light microscopical level of chromosome aberrations. Several prelimary reports about the different topics have been published.

### 123. THE USE OF ISOENZYME PROFILES OF LYSOSOMAL HYDROLASES IN DISTINGUISHING BETWEEN DIFFERENT TYPES OF LEUKEMIA

*Ellis, R. B.,* Medical Research Council, Clinical Genetics Unit, Inst. of Child Health, *30 Guilford St., London WC1N 1EH, England, United Kingdom*

OBJECTIVES: Ellis et al. (New Engl. J. Med. 1978, 298, 476-480) have recently shown that a raised activity of hexosaminidase isoenzyme 'I' is found in extracts of leukemic cells from children with the common form of childhood acute lymphoblastic leukemia but not in other forms of acute leukemia. This finding is to be assessed for its potential usefulness in the differential diagnosis of patients at presentation, in the early detection of relapse, and in prognosis. Also, the isoenzyme profiles of other lysosomal hydrolases will be studied in leukemic cells.

APPROACH: Isoenzyme profiles are determined using automated micro-column anion-exchange chromatography, and an attempt to prepare a specific hexosaminidase 'I' antiserum is being made.

PROGRESS: The investigation of a larger number of patients has confirmed the original findings. Pre-T ALL cells do not express hex 'I' and pre-B ALL cells have a lower activity than other ALL cells. Preliminary findings suggest that the acid phosphatase isoenzyme pattern is distinctive in T-ALL.

### 124. CELLULAR ENZYME CHANGES IN CHILDHOOD LEUKEMIA

*Dunn, N. L., Wolf, B., Mohanakumar, T.,* Virginia Commonwealth University, Medical College of Virginia, Dept. of Pediatrics, *1200 E. Broad St., Richmond, Virginia,* 23298, United States of America

The possibility that tumor-specific enzyme/isoenzyme changes exist in leukemic cells is being explored in this research proposal by studying the enzyme acivities and isoenzyme profiles of hexosaminidase, pyruvate kinase and isocitric dehydrogenase in the lymphoblasts of children with ALL. All 3 enzymes under study were selected because they have isoenzyme forms coded for on chromosome 15; thus the pattern of changes found may provide clues to the nature of the leukemia transformation process(es). Serial follow-up of patients and comparison to values obtained with normal resting lymphocytes and normal lymphocytes induced to undergo blastogenesis are being used to determine the leukemia-specificity and, therefore, the clinical usefulness as tumor markers of any differences discovered.

PROGRESS: This study has been under way for less than 1 year, during which time 16 patients and 27 pediatric controls have been studied. Results are too preliminary for publication at this time.

### 125. RELATIONSHIP BETWEEN SURFACE MARKERS AND CYTOCHEMICAL STAINS IN ALL

*Donoso, J., Taboada, H., Grebe, G.,* Universidad Catolica de Chile, Depto. de Pediatria, *Casilla de Correo #89, Puente Alto, Chile*

OBJECTIVE: To determine the relationship between these two methods of classifying acute lymphatic leukemia in children, with emphasis on determining the relationship between subpopulations of T leukemias and acid phosphatase stain.

METHOD: Upon diagnosis, studies are performed on membrane receptors using the rosette formation test (T lymphocytes) and the synthesis of immunoglobulins (B lymphocytes), with which the leukemia is classifed into T-B-null.

Then studies are performed with cytochemical stains (PAS acid phosphatase), and clinical studies are performed (thoracic X-ray, etc.).

The evolution of the child is followed to observe the behavior of the various subgroups, with special focus on the 'null' acid phosphatase positive leukemias.

PROGRESS: This study has been underway for one year, during which time 35 children have been studied. It has been determined that 90% of the T leukemias are acid phosphatase positive. The significance of the other subgroups remains to be seen.

### 126. MATURATION OF T-LYMPHOCYTES IN BONE MARROW FROM NORMALS AND FROM PATIENTS WITH DIFFERENT TYPES OF ACUTE LYMPHOBLASTIC LEUKEMIA

*de Vaan, G. A., Bakkeren, J. A., Schretlen, E. D.,* Katholieke Universiteit Nijmegen, Dept. of Pediatrics, *Erasmuslaan 4, Nijmegen, Netherlands*

OBJECTIVE: Unbridled proliferation and the lack of normal cell maturation are essential characteristics of acute leukemia. The different subtypes of acute lymphoblastic leukemia (ALL) may be correlated with the various stages of maturation of the lymphoid pattern in normal bone marrow. Fractionation of bone marrow via gradient density centrifugation of normal and leukemic bone marrow may provide information for a comparative study.

APPROACH: Various methods of density gradient centrifugation are investigated to fractionate normal and leukemic bone marrow. A discontinuous bovine serum albumin (BSA) gradient and a continuous Percoll gradient are studied. For

identification of the different subfractions, besides the immunological characteristics and antigenic determinants on the cell surface, the proliferative capacity of the cells is also determined. Leukemic bone marrow cells from children with various lympho- and myelo-proliferative diseases are included in the study.

PROGRESS: By centrifugation over a discontinuous BSA density gradient good reproducibility of the partition of the bone marrow cell population was obtained with a control group of 12 children with ALL in complete remission and after cessation of all antileukemic therapy. In 9 children with various lympho- or myelo-proliferative malignancies, similar fractionation revealed a different cell partition pattern as compared with the control group. Similar experiments using a continuous Percoll gradient are in progress.

BIBLIOGRAPHIC REFERENCES: Bakkeren, J.A.J.M., de Vaan, G.A.M., Utility of density gradient centrifugation of leukemic bone marrow. Med. Ped. Oncol., 8,83-96 (1980).

## 127. COLONY FORMATION IN VITRO OF LEUKEMIC BLASTS IN ACUTE CHILDHOOD LEUKEMIA

*de Koning, J., van't Veer Korthof, E., van Weel Sipman, M. H.*, Academisch Ziekenhuis Leyden, Dept. of Pediatrics, *Rijnsburgerweg 10, 2333 AA Leyden, Netherlands*

OBJECTIVES: To culture leukemic blasts of acute leukemia cells of children; identification of blasts by immunological measures in order to determine the T-B or Null origin of the cultured cells.

## 128. THE IMMUNE SYSTEM IN DOWN'S SYNDROME AND ITS RELATIONSHIP TO MALIGNANCY

*Levin, S., Handzel, Z. T., Altman, Y. N., Hahn, T. C., Idar, D. A., Or, A. S., Trainin, N.*, Kaplan Memorial Hospital, Dept. of Pediatrics, *P.O.B. 1, Rehovot, Israel*

Evaluation of immune status (thymic dependent) in Down's Syndrome, known to have an increased incidence of lymphatic leukemia, is being undertaken.

## 129. MONITORING FAMILIAL MEDULLARY CARCINOMA OF THE THYROID

*Genel, M., Burrow, G. N., Landsberg, L., Clinton, B., Gertner, J. M., Page, S.*, Yale University, School of Medicine, Dept. of Pediatrics, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

The syndrome of medullary carcinoma of the thyroid, pheochromocytoma and parathyroid gland hyperplasia or Multiple Endocrine Neoplasia Syndrome-Type II, is transmitted as an autosomal dominant trait with an approximate 50% chance of occurrence in children of an affected parent. In a large New Haven kindred, comprised of more than 120 members living in a close proximity to New Haven, annual screening of individuals 4 years of age and older has been performed for the past 4 years in the ambulatory facilities of the Adult (General) and Children's Clinical Research Centers, Yale-New Haven Medical Center. To December 1979, pentagastrin provocation, 0.5 mcg/kg and measurement of calcitonin by immunoassay was used as the screening procedure for medullary carcinoma. Positive responses were seen only in individuals previously known to have disease. As of 12/1/79 the procedure was altered to use a combined pentagastrin-calcium infusion based on the above recent data. Screening for parathyroid disease is performed simultaneously with the infusion using total and ionized calcium, alkaline phosphatase and immunoreactive parahormone levels. Urinary catecholamines are obtained on 24-hour collections and assayed in the laboratory of Dr. Lewis Landsberg, Beth Israel Hospital, for pre-symptomatic detection of pheochromocytoma.

Genetic analysis of the kindred performed during the year has succeeded in identifyiing one of the four main branches of the kindred as almost certainly not at risk based on absence of the disease through 4 generations and normal testing via pentagastrin provocation in more senior members of the branch. It is hoped that further analysis of the family pedigree using the clinical histories and responses to provocation will serve to eliminate other members of the family from active follow-up as 'at risk' for MEN Type II.

## 130. STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

*Becker, K. L., Silva, O. L.*, U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

Our main activity involves the study of the hormone calcitonin. We are currently exploring the physio-chemical state of calcitonin in the blood. We have developed a sensitive radioreceptor assay for the hormone, in order to determine which of the heterogenous serum fractions react with receptor. We have also developed a radioimmunoassay for calcitonin in the urine, and have found it to be of considerable value in the diagnosis of medullary thyroid cancer. We have determined urine calcitonin in normal children ages 2-15 years; children up to age 13 have higher values than adults. Children undergoing a diagnosis of medullary thyroid cancer must be compared by sex and age. In addition, we are utilizing serum and urinary calcitonin as a label for lung cancer and breast cancer.

We have found that large amounts of calcitonin exist in several tissues other than the thyroid gland; the gel filtration of this extrathyroidal calcitonin is identical to the monomer. In exploring its presence in muscle we have found that exercise induces a change in the excretion pattern of urinary calcitonin. In our study of pulmonary calcitonin we have localized calcitonin in the Kultschitzky cell of the lung by immunoperoxidase staining. We are pursuing our studies of muscle and lung calcitonin.

## 131. BENIGN AND MALIGNANT FIBROUS LESIONS IN CHILDREN

*Diaz, F., Barbosa, G.*, Instituto Nacional de Cancerologia, Seccion de Patologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the anatomopathological and clinical characteristics of benign and malignant fibrous lesions in children treated in the Instituto Nacional de Cancer, Colombia.

MATERIAL: The clinical histories of children with confirmed diagnoses of benign or malignant fibrous lesions treated between January 1963 and December 1974 will be studied by retrospective analysis. (Translated)

## 132. LIPOMAS AND LIPOSARCOMAS IN CHILDREN

*Castro, E., Martin, F., Calderon, O.*, Instituto Nacional de Cancerologia, Seccion de Patologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the anatomopathológical and clinical characteristics of lipoma and liposarcoma in children treated in the Instituto Nacional de Cancer, Colombia.

MATERIAL: The clinical histories of children with confirmed diagnosis of lipoma and/or liposarcoma treated between January 1963 and December 1974 will be studied by retrospective analysis. (Translated)

## 133. SARCOMA OF THE SOFT TISSUE IN CHILDREN

*Martin, F., Barbosa, G., Jimenez, M.*, Instituto Nacional de Cancerologia, Seccion de Patologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the anatomopathological and clinical characteristics of soft tissue sarcomas in children treated in the Instituto Nacional de Cancer, Colombia.

MATERIAL: The clinical histories of children with confirmed diagnoses of soft tissue sarcoma treated between January 1973 and December 1974 will be studied by retrospective analysis. (Translated)

## 134. OVARIAN TUMORS IN YOUNG GIRLS AND ADOLESCENTS

*Rodriguez, A., Klausz, E., Castro, E.*, Instituto Nacional de Cancerologia, Seccion de Patologia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To determine the anatomopathological and clinical characteristics of ovarian tumors in young girls and adolescents treated in the Instituto Nacional de Cancer, Colombia.

MATERIAL: The clinical histories of children with confirmed diagnoses of ovarian tumor treated between January 1966 and December 1980 will be studied by retrospective analysis. (Translated)

### 135. STUDY OF VALUE OF CLINICAL AND HISTOLOGIC STAGING AND A PHASE III STUDY OF CHEMOTHERAPY OF HISTIOCYTOSIS X IN CHILDHOOD

*Ekert, H., Waters, K., Smith, P. J.,* Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

OBJECTIVES: 1. To determine prospectively whether clincial and histological staging of patients with Histiocytosis X has prognostic and therapeutic significance. 2. To test the efficacy of 2 chemotherapy regimens in treatment of Histiocytosis X.

HISTOLOGIC TYPE AND CLINICAL STAGE: Children with histologically proven Histiocytosis X are staged clinically using Lahey's criteria and histologically using Newton and Hamoudi's criteria.

TREATMENT MODALITIES AND AGENT: Regimen 1. Oral chlorambucil 5 mg/m2/D p.o. PNSL 40 mg/m2/D p.o. D1 to 42; VBL 6.5 mg/m2/wk i.v. for 8 wks, MTX 20 mg/m2/wk p.o. as a single dose started on D2 and continue for 6 months; PNSL/VBL pulses on D70 and each 28 days after that point receives PNSL 40 mg/m2 D for 1 week and VBL 6.5 mg/m2/wk x 2.

PROTOCOL: Not controlled or randomized.

PRESENT STATUS: 24 children entered. 80% disease-controlled or -free survival. Median follow-up 3 years.

### 136. CELL SURFACE ANTIGENS OF CHILDHOOD BRAIN TUMORS

*Zelter, P. M.,* University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Pediatrics, *7703 Floyd Curl Dr., San Antonio, Texas,* 78284, United States of America

OBJECTIVE: The overall objective of this project is to develop specific and sensitive serologic assays for brain tumor antigens which may provide improvements over techniques currently available for diagnosis, classification and monitoring of these neoplasms in children.

APPROACH: CSA (tumor related, fetal, differentiation type) of these brain tumors will be identified and later characterized, using serologic and molecular techniques which were developed in this laboratory. Next, three types of investigations using these CSA will be implemented: 1) determination of tumor CSA phenotype, 2) quantitation of soluble CSA in cerebrospinal fluid, serum, and/or urine by radioimmunoassay, and 3) determination of human anti-CSA antibody responses. The value of these tests for diagnosis, prognosis, and therapeutic assessment will be determined by correlation with clinical parameters.

### 137. BLADDER CARCINOMA (CHILDREN)

*Bing, D. H.,* Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts,* 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 138. IDENTIFICATION, PURIFICATION, CHARACTERIZATION AND CLINICAL APPLICATIONS OF TUMOR-SPECIFIC ANTIGENS IN VARIOUS HUMAN TUMORS

*Kurata, Y., Okada, S.,* Kanazawa University, Cancer Research Inst., Dept. of Pathophysiology, *13-1 Takaramachi, Kanazawa 920, Ishikawa-ken, Japan*

The principal goal of this research program is to study the role of the tumor-specific antigens in diagnosis and treatment of human cancers.

The insoluble fractions of a variety of human tumors were partially solubilized with desoxycholate and soluble fractions, after partial purification by gel filtration, were used to raise xenogeneic antisera. Using such antisera, the tumor-specific antigens of nephroblastoma, transitional cell carcinoma, and renal cell carcinoma were successfully identified on the tumor cell membranes. The analysis of lung cancers, pancreatic carcinoma, and gastric carcinoma is in progress. The treatment of patients with tumor by the immune RNA which recognized the tumor-specific antigen is under way.

### 139. A NEW INTERFERON SYSTEM ASSAY IN PATIENTS WITH MALIGNANCIES AND SUSPECTED MALIGNANCIES

*Levin, S., Hahn, T.,* Kaplan Memorial Hospital, Dept. of Pediatric Research, *P.O.B. 1, Rehovot, Israel*

The object of this study is to evaluate various parameters of the interferon system, both extracellular and intracellular, in patients with malignancies and those suspected of having malignancy. A combined assay which studies the interferon levels in the blood of the patient and the ability of the patient's polymorphonuclear monocytes (PBMC) to produce both type I and type II interferon when appropriately stimulated and evaluates the anti-viral status of the patient's PBMC, will be performed in all cases. Fifty to one hundred children and adults with neoplastic disease or suspected disease will be studied and correlations will be made between the assay and the clinical status and course of the patients. Preliminary studies indicate that this assay system may be useful in indicating which patients are likely to respond to interferon therapy. These studies in patients receiving interferon therapy have shown the practicability of this research. The immuno-regulatory effect of interferon used in the treatment of the patients is also being studied.

### 140. DETERMINATION, IN PEDIATRICS, OF THE EXTENT OF CANCER BY MEANS OF LYMPHADENOGRAPHY

*Papendieck, C. M., Ostrowski, I., Luis, D. R.,* Hospital de Ninos de Buenos Aires, Dept. Cirugia, *Gallo 1330, 1425 Buenos Aires, Capital Fed., Argentina*

OBJECTIVES: To determine lymphatic nodal and extranodal involvement in the metastases of tumors in childhood, and the retrograde or anterograde spreading of primitive tumors of the lymphatic system, by means of the transnodal lymphography.

APPROACH: Study of patients from 0-14 years of age registered at CETNI (Centro de Estudio y Tratamiento de los Tumores en la Infancia -Hospital de Ninos) with tumoral pathology, and with the following aims: diagnosis, differential diagnosis, and diagnosis of the degree of extension.

### 141. PEDIATRIC TUMOR RESOURCE

*Kaizer, H.,* Johns Hopkins University, School of Medicine, Dept. of Oncology, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

OBJECTIVES: Provide samples of freshly isolated sterile tumor specimens from both solid tumor and acute leukemia patients in a form suitable for tissue culture. Preserve residual biopsied tissue for distribution for biochemical studies. Preserve tumor tissue obtained at necropsy under non-sterile conditions for distribution for biochemical studies. Provide samples of secondary cultures from successfully cultured tumor specimens. Preserve and distribute to the SVCP Serum Bank serum obtained as diagnostic or evaluative blood tests are performed.

## B. PROGNOSTIC FACTORS IN CHILDHOOD CANCER

### 142. FURTHER DEVELOPMENT OF A TEST WHICH DETECTS RESIDUAL DISEASE AND PREDICTS RELAPSE IN CHILDREN WITH ALL

*Mott, M. G., Gentle, T.,* University of Bristol, Royal Hospital for Sick Children, Dept. of Child Health, *Bristol, England, United Kingdom*

OBJECTIVE: To determine whether it is possible to predict leukemic relapse by measuring peripheral blood lymphocyte blastogenesis induced by bone marrow blasts at subclinical levels.

APPROACH: A pilot study of co-cultivation of peripheral blood lymphocytes and bone marrow suggested that relapse could be predicted by measuring the stimulation ratio of the lymphocytes. The mechanism of this reaction and its verification in a larger series form the basis of this research study.

PROGRESS: This is a new project.

**143. THE USE OF ISOENZYME PROFILES OF LYSOSOMAL HYDROLASES IN DISTINGUISHING BETWEEN DIFFERENT TYPES OF LEUKEMIA**

*Ellis, R. B.*, Medical Research Council, Clinical Genetics Unit, Inst. of Child Health, *30 Guilford St., London WC1N 1EH, England, United Kingdom*

The summary for this project is under entry no. 123.

**144. LEUKEMIA MONITORING BY FLOW CYTOMETRY/ SORTING**

*Andreeff, M.*, Sloan Kettering Inst. for Cancer Research, Dept. of Pathology, *410 E. 68th St., New York, New York*, 10021, United States of America

The objective of the proposed study is to monitor a large number of acute leukemias of adults and children by flow cytometry/cell sorting techniques. These data, to be determined serially through all stages of disease, will provide a more precise means of evaluating treatment protocols and predicting relapse. Aneuploidy, present in more than 50% of the childhood and in 16% of the adult leukemias, will serve as a marker. Flow cytometric DNA-RNA measurements, also useful for the classification of leukemias, will determine the leukemic DNA stemline, and thus detect aneuploidy. Patients with aneuploidies will be followed serially during induction, consolidation and maintenance therapy and thereafter. Identification of very low numbers of aneuploid leukemic cells will be performed in three different ways, 1) multiparameter flow-cytometry measurements of more than 1 million mononuclear cells per sample (blood and bone marrow); 2) enrichment of leukemic cell populations by 1xG velocity sedimentation and flow-cytometry; and 3) combined flow-cytometric cell sorting-autoradiographic techniques to distinguish hyperdiploid G1 leukemic cells from normal hematopoietic S cells. In addition, differences in chromatin structure of intact leukemic vs. normal hematopoietic cells, as determined by flow-cytometric measurements of acridine orange binding after acid and thermal denaturation, will be used to identify small number of diploid as well as aneuploid leukemic cells. These results will be compared with morphological/cytochemical findings by light microscopy and with special studies conducted in other laboratories.

**145. PEDIATRIC HEMATOPOIETIC MALIGNANCIES - PROGNOSTIC FACTORS IN CHILDHOOD LEUKEMIA**

*Murphy, M. L.*, Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

**146. NEGATIVE FEEDBACK REGULATION OF GRANULOPOIESIS BY LACTOFERRIN DURING LEUKEMIA AND MYELODYSPLASIA**

*Broxmeyer, H. E., DeSousa, M., Nishiya, N., Meyers, P. A.*, Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

The capacity to assay hematopoietic committed stem cells in humans and factors which regulate their growth allows us to investigate normal and abnormal hematopoiesis in vitro and in vivo. We believe that defects in negative feedback regulation of granulocytic-monocytic stem cells are important in the development and progression of acute and chronic leukemia and myelodysplasia. We propose to use in vitro and in vivo approaches to study in depth a cell-free inhibitory activity we have recently reported and which we have now identified as lactoferrin. Lactoferrin is a well-characterized iron-binding glycoprotein which is presently available in purified form. Defects in the lactoferrin negative feedback regulation of granulopoiesis are probably involved in the pathogenesis and progression of leukemia and myelodysplasia.

The prognostic and diagnostic potential of these regulatory interactions will be explored. Large numbers of patients will be screened for the quantity and qualitative effectiveness of lactoferrin and for the response of normal cells and cells of patients to lactoferrin. This may allow us to detect residual leukemic cells during remission and may be a sensitive means to detect acceleration to the terminal phases of acute leukemia.

Normal and leukemic mice will be used to determine the in vivo action and significance of lactoferrin with regard to disease progression. Biophysical and immunological cell-separation procedures will be used to further elucidate the subpopulations of cells elaborating and responding to lactoferrin. A knowledge of the exact regulatory mechanisms and their lesions during disease will allow us to develop methods in an attempt to counteract the 'pathological' interactions and enhance physiological mechanisms in vitro and in vivo.

**147. CALCIUM AND PHOSPHORUS METABOLISM IN LEUKEMIC CHILDREN**

*Zannos Mariolea, L., Lapatsanis, P., Haidas, S., Benetos, S., Dendaki Svolaki, C.*, University of Athens, Dept. of Pediatrics, *Odos Panepistimiou 30, Athens 143, Greece*

Bone lesions are observed in leukemic children. This observation led us to study calcium (Ca) and phosphorus (P) metabolism in leukemic patients. All patients do not receive any food for at least twelve hours before the biochemical investigations (overnight). They empty their bladders in the morning and then urine is collected for three hours and at the same time blood samples are taken. The following biochemical tests are performed: a) serum Ca, b) serum P, c) urine phosphorus (P) to urine creatinine (Cr) concentration ratio (UP:UCr) and d) urine calcium (Ca) to urine creatinine concentration ratio (UCa:UCr). Serum Ca, P, urinary Ca, P and Cr were measured as previously reported. Thirty-one (31) leukemic children have been examined. So far our findings indicate that a) there is an increase in net bone resorption, b) there is a decrease in renal tubular reabsorption of phosphorus, and c) glomerular penetration rate is normal.

The study is in progress.

**148. CELL KINETICS OF NORMAL AND NEOPLASTIC HUMAN HEMATOPOIETIC AND IMMUNOLOGICALLY ACTIVE CELLS**

*Wagner, H. P.*, Universitat Bern, Inst. for Clinical & Experimental Cancer Research, *Tiefenauspital, 3004 Bern, Switzerland*

OBJECTIVE: Development of methods for combined immunological, cytochemical, and cytokinetic studies on single bone marrow and peripheral blood lymphoid cells. Investigation of children with ALL and lymphoma before, during and after treamtent.

APPROACH: Ficoll isolation lymphoid cells are pulse-labeled in vitro with radioactive specific DNA precursors; exposed to fluorescent, specific antibodies and sheep erythrocytes; centrifuged on slides; mapped with a computer-controlled scanning microscope fluorometer; evaluated for fluorescence; stained for unspecific acid esterases; evaluated for morphology and esterase reaction; processed radioautographically and evaluated for nuclear labeling.

PROGRESS: Normal and neoplastic lymphoid blood and bone marrow cells are classified using the parameters listed above. The number of proliferating and non-proliferating cells in the different subpopulations of lymphoid cells from normal individuals is compared to the number of similar cells from children with ALL or lymphoma.

**149. LYMPHOCYTE ONTOGENY IN CHILDHOOD ALL**

*Dosch, H., Gelfand, E. W.*, Hospital for Sick Children, Division of Immunology, *555 University Ave., Toronto, Ontario*, M5G 1X8, Canada

In a differentiating immune system substantial heterogeneity is expressed at the cellular level with respect to surface markers, metabolism, adequate triggers for differentiation and functions and their specificities. This heterogeneity seems mirrored in ALL, where one or many differentially expressed parameters may direct or signal course and prognosis. With the combination of new techniques, including the use of thymopoietic induction regimen, a number of assays for immunoregulatory functions, the development of monoclonal antibodies against surface glycoproteins and the study of purine metabolic pathways in leukemic cells, we may be able to dissect the developing immune system more comprehensively, derive new patient groupings in ALL and eventually recognize prognostic parameters in this leukemia. Our studies will focus on the active functions and the requirements for growth and differentiation of leukemic cells, in fact, consider them a functional part of the leukemic host. In addition to dissecting heterogeneity among leukemic patients, these studies promise new insights into some

of the mechanisms which must direct response to therapy and its failure and they may delineate new strategies for therapy.

### 150. LYMPHOCYTE DIFFERENTIATION IN CHILDHOOD LEUKEMIA

*Kaplan, J.*, Children's Hospital of Michigan, *3901 Beaubien St., Detroit, Michigan*, 48201, United States of America

This project seeks to investigate the nature of the cells of origin of acute childhood leukemias and the factors which govern their differentiation and proliferation. We plan to increasingly focus on the possibility that natural killer (NK) cells are committed pre-thymic T cell precursors which function as regulators in the hemopoietic system and as such mediate resistance to hemopoietic tumors. We will attempt to confirm that NK cells regulate EBV-induced B cell proliferation and examine by co-cultivation experiments the influence of various human T cell subpopulations on myelopoiesis and erythropoiesis. In addition we will attempt to determine the prognostic significance and therapeutic implications of all phenotypes defined by a panel of cell surface markers and to develop a mouse hybridoma which produces monoclonal antibody to human terminal transferase, an extremely useful leukemia cell marker.

BIBLIOGRAPHIC REFERENCES: Kaplan, J., and Callewaert, D.M. Expression of human T lymphocyte antigens by natural killer cells. J. Natl. Cancer Inst. 60:961-964, 1978. Callewaert, D.M., Lightbody, J.L., Kaplan, J., Jaroszewski, J., Peterson, W.D., Jr., and Rosenberg, J.C. Cytotoxicity of human peripheral lymphocytes in cell-mediated lympholysis: antibody-dependent cell-mediated lympholysis and natural cytotoxicity assays after mixed lymphocyte culture. J. Immunol. 121:81-85, 1978.

### 151. HUMAN HISTIOCYTOSIS X - HISTOGENESIS - PROGNOSIS - ETIOLOGY

*Nezelof, C., Rousseaumerck, M. F., Jaubert, F.*, Inst. National de la Sante et de la Recherche Medicale, Pediatric Pathology Unit, *149, Rue de Sevres, c/o Hop. Enfants Mal, 75730 Paris Cedex 15, France*

OBJECTIVE: To characterze the origin and the properties of the proliferating cells in Histiocytosis X; to define the criteria of the prognosis in disseminated forms; and to try to characterize some etiologic factors.

APPROACH: Tissue culture of eosinophilic granulomas; electron microscopy of various forms of Histiocytosis X: comparative studies of HX cells and Langerhan's cells; and epidemiologic studies of children with disseminated Histiocytosis X.

PROGRESS: Presence of an ultrastructural marker (X body or Langerhan's body) within the cytoplasm of HX cells; presence of surface receptors for IgG and C3 on the membrane of HX cells. Preliminary results are reported in Journal of Pathology.

### 152. STUDY OF VALUE OF CLINICAL AND HISTOLOGIC STAGING AND A PHASE III STUDY OF CHEMOTHERAPY OF HISTIOCYTOSIS X IN CHILDHOOD

*Ekert, H., Waters, K., Smith, P. J.*, Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

The summary for this project is under entry no. 135.

### 153. IMMUNE RESPONSE OF CHILDREN TO NEUROBLASTOMA

*Seeger, R.*, University of California, Los Angeles Campus, School of Medicine, Dept. of Pediatrics, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

There is a well recognized need to improve therapy for two-thirds of children with neuroblastoma. This investigation will generate monoclonal antibodies to neuroblastoma associated fetal and/or neural cell surface antigens (CSA), to neurotransmitter-synthesizing enzymes, and to neuroblastoma produced auto-stimulatory growth factors. Our approach is to develop a panel of antibodies because the simultaneous use of two or more antibodies is likely to improve many aspects of immunodiagnosis and immunotherapy; multiple antibodies will be particularly useful in dealing with the problem of tumor heterogeneity. Monoclonal antibodies will be used for clinical diagnostic and preclinical therapeutic investigations. Clinical diagnostic studies will determine (1) the prognostic value of antigenic phenotyping at diagnosis and (2) the ability of immunoenzyme and immunofluorescent analysis of bone marrow and radioimmunoassay of serum to accurately assess tumor burden 25 weeks after diagnosis. Preclinical antibody therapy studies will use neuroblastoma cell lines growing in vitro and in athymic nude mice to investigate (1) antibodies that cooperate with human complement and effector cells to mediate complement dependent or antibody dependent cellular cytotoxicity and (2) antibodies that affect proliferation and survival of neuroblastoma cells independent of complement and effector cells. Having identified antibodies that are effective alone, combinations will be tested to identify those that are additive or synergistic. If successful, these preclinical studies could be the basis for designing clinical antibody therapy for neuroblastoma. These investigations of clinical immunodiagnosis and preclinical antibody therapy should significantly contribute to our long-term aim of achieving optimal therapy for children with neuroblastoma.

### 154. CHILDHOOD NEUROBLASTOMA - ANTIGENIC CHARACTERISTICS

*Casper, J. T., Keller, R., Hodach, A., Lauer, S. J.*, Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin*, 53233, United States of America

The prognosis of neuroblastoma, one of the most common childhood cancers, has not improved over the last two decades. It is almost universally fatal in older children with disseminated disease. In contrast, neuroblastoma of infants younger than one year may spontaneously remit, or it is frequently controlled and cured with current therapy. The long-term goal of this proposal is to critically define these factors and to determine their role in the clinical characteristics and therapeutic response of childhood neuroblastoma. Specifically we will determine if lymphocyte or serum mediated cytotoxicity against neuroblasts is due to normal differentiation antigens or to tumor specific antigens, compare the cytotoxicity of bone marrow, lymph node and blood lymphocytes against autologous or allogeneic neuroblasts, and establish if alpha-fetoprotein, detected on established neuroblastoma cell lines, is also expressed on viable neuroblasts from patients and investigate the effect of neuroblast-associated alpha-fetoprotein on host immune response. Systematic studies of these parameters should establish the biological differences between neuroblastoma of younger and older children and provide the knowledge required for the development of effective therapy.

### 155. CHILDHOOD BRAIN TUMOR CONSORTIUM

*Gilles, F. H.*, Harvard University, Boston Campus, Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

A consortium of ten institutions located in North America has been organized, which utilizes the efforts of neuropathologists, pediatric pathologists, a neuroepidemiologist, neurosurgeons, and biostatisticians in a study of childhood brain tumors.

Our principal goal is to obtain accurate prognostic information for tumors at specific sites for the design of therapy for individual children, and for studies of competing therapies. The estimated data base from the ten institutions in the consortium is between 3,000 and 3,400 children. We will use the first surgical sample for the assessment of the prognostic significance of individual histologic patterns and antecedent clinical features. We will use two classifications, that of the World Health Organization, and another one which uses the biologic characteristics of clustering of histologic patterns and life tables. We will choose which of these classifications provides the most accurate prognostic information for tumors at each site within the brain. This information will be entered into the computer via interactive programs which will provide: 1) specific prognostic information for tumors at each of several sites within the brain for individual patient care decisions by any pathologist or neurosurgeon, and 2) prognostic information for the design of studies of competing therapies.

BIBLIOGRAPHIC REFERENCES: Gilles, F.: Prognosis in cerebellar tumors. Lab. Invest. 40:4, 1979.

### 156. METABOLIC STUDY OF ADULT AND PEDIATRIC CANCER PATIENTS

*Holroyde, C. P., Reichard, G. A., Axelrod, R. S., Skutches, C. L., Haff, A. C.,* Lankenau Hospital, Oncology Research Unit, *Lancaster & City Line Aves., Philadelphia, Pennsylvania,* 19151, United States of America

The overall objective of this research is to investigate glucose and lactate metabolism in hospitalized patients with malignant solid tumors, particularly colo-rectal cancer. Using isotope tracer infusion techniques, the production, oxidation and recycling of glucose via lactate will be measured under standardized conditions. These data will be correlated with the presence or absence of carbohydrate intolerance following an oral glucose load. Preliminary data on the metabolic response of cachetic patients to an ingested protein meal will be extended and incorporated into planned work with alanine turnover studies. These data on abnormal responses to ingested protein may provide a rational basis from which improvements, concurrent therapy and support may be achieved.

BIBLIOGRAPHIC REFERENCES: Lactate metabolism in patients with metastatic colo-rectal cancer. Holroyde, C.P., Axelrod, R.S., Skutches, C.L., Haff, A.C., Paul, P., and Reichard, G.A. Cancer Research 39:4900-4904, 1979. Carbohydrate metabolism in cancer cachexia. Holroyde, C.P. and Reichard, G.A. Accepted for publication. Cancer Treatment Reports. 1981.

### 157. A NEW INTERFERON SYSTEM ASSAY IN PATIENTS WITH MALIGNANCIES AND SUSPECTED MALIGNANCIES

*Levin, S., Hahn, T.,* Kaplan Memorial Hospital, Dept. of Pediatric Research, *P.O.B. 1, Rehovot, Israel*

The summary for this project is under entry no. 139.

### 158. CELL-MEDIATED CYTOTOXICITY IN CHILDREN WITH NEOPLASMS

*Yu, A. L.,* University of California, San Diego Campus, School of Medicine, Dept. of Pediatrics, *P.O. Box 109, La Jolla, California,* 92093, United States of America

Recently, we demonstrated for the first time in the human system the coexistence of tumor specific cytotoxic and suppressor lymphocytes. We now propose to: (1) Determine the clinical significance of cytotoxic and suppressor cells by a prospective study of patients' lymphocytes throughout their clinical course, (2) elucidate the mechanisms of interaction between cytotoxic and suppressor lymphocytes by determining the tumor specificity of suppression, the possible involvement of soluble-suppressive factor and the possible modulation of the interactions by thymic-hormonal factor and various drugs, (3) differentiate tumor-specific cytotoxicity from natural cytotoxicity by separating the effector cells responsible for these two types of cytotoxicity and the use of various drugs to eliminate natural cytotoxicity.

## IV. CLINICAL THERAPY OF PEDIATRIC NEOPLASMS

## A. THERAPY OF LEUKEMIA, LYMPHOMA AND HISTIOCYTOSIS

### 159. L-ASPARAGINASE IN REMISSION INDUCTION OF ALL IN CHILDHOOD

*Wehinger, H.,* Kinderklinik am Stadtkrankenhaus, *Moenchebergstrasse 41, 3500 Kassel, Hessen, Federal Republic of Germany*

OBJECTIVE: To see if L-asparaginase is useful in remission induction of ALL as a third drug in addition to vincristine and prednisone when given at an interval after vincristine. (With simultaneous application there might be negative interference between L-Asp and VCR, because L-Asp arrests cells in the late S-phase, thus preventing the cells from proceeding to M to become vulnerable by VCR).

APPROACH: Thirty patients were randomized to receive either VCR plus Pred or VCR plus Pred plus L-Asp as an induction regimen for ALL in children. Asparaginase was given 24 hours after vincristine once weekly in a single infusion dose of 1000 U/kg. Meningosis prophylaxis and maintenance were performed the same way in both groups.

PROGRESS: After an observation time of 12-45 (mean 30) months no difference is seen between the two groups.

### 160. RESEARCH WITH ENZYMES AS ANTITUMOR AGENTS

*Holcenberg, J. S., Camitta, B., Kien, C. L., Anderson, T.,* Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin,* 53233, United States of America

The aim of this proposal is to further advance Acinetobacter glutaminase-asparaginase as an anti-tumor agent by experiments designed to extend our initial findings. The important areas for further study are: 1) clinical trials as a single agent, 2) rational combination chemotherapy and 3) mechanisms of toxicity. The following specific aims address each of these areas: 1) Clinical trials will concentrate on patients with acute myelogenous leukemia, chronic lymphocytic leukemia and solid lymphoid malignancies. 2) Rational combination chemotherapy will test SAGA with melphalan by the belly bath technique for tumors confined to the peritoneal cavity. 3) Preclinical studies in animals will investigate the mechanisms of central nervous system toxicity and inhibition of protein synthesis in an effort to find methods to reverse or prevent these problems without decreasing antitumor effectiveness.

### 161. BCG VACCINATION AND LEUKEMIA

*Katz, L., Steinitz, R.,* Israel Center for Registration of Cancer & Allied Diseases, *18-20 King David St., Jerusalem 91000, Israel*

The possibility that the reported non-specific immunity conferred by BCG may have some influence in the prevention of leukemia in children is being investigated. In Israel a unique opportunity presents itself for studying the incidence of leukemia in BCG vaccinated children and in a non-vaccinated control group: since 1955 routine BCG vaccination of newborns has been carried out in all maternity wards in Israel - with the exception of the Jerusalem hospitals, where it was never introduced. The incidence of leukemia in children born in Israel since 1955, diagnosed after 1960 (the year the Israel Cancer Registry was founded) and up to the age of ten will be studied. Two hundred and sixty-three cases of leukemia in children have been identified. Their places of birth are now being ascertained.

### 162. CHEMOIMMUNOTHERAPY (BCG) CONTROLLED TRIAL IN ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDHOOD

*Rice, M. S., Leahy, M. A., Toogood, I. R.,* Adelaide Children's Hospital, *72 King William St., Adelaide, S. Australia 5066, Australia*

OBJECTIVES: 1. To investigate whether intermittent chemotherapy, combined with immunotherapy, prolongs the duration of the first complete remission, compared with intermittent chemotherapy alone. 2. To investigate whether intermittent chemotherapy, combined with immunotherapy, results in longer survival than intermittent chemotherapy alone. 3. To determine the effects of these regimens on immunological function and on the incidence of infective and other complications.

APPROACH: A cooperative study (Australian Cancer Society Childhood Leukemia Study Group) using a standard protocol. Chairman of Study Group is Dr. H. Ekert, Royal Children's Hospital, Parkville, Victoria, 3052.

### 163. CONTROLLED CLINICAL TRIAL (PHASE III) OF CHEMOIMMUNOTHERAPY IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA (ALL)

*Ekert, H., Jose, D. G., Tauro, G. P., Waters, K. D., Matthews, R. N., Matthews, J.,* Royal Children's Hospital, Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVES: 1) Compare duration of first complete remission maintained with intermittent chemotherapy and BCG compared with intermittent chemotherapy only. 2) Determine the effects of these regimens on immunologic function and infective complications.

HISTOLOGICAL TYPE AND CLINICAL STAGE: Children with morphologic and cytochemical diagnosis of ALL are stratified on the basis of age, organomegaly and total white cell count into good prognosis (WCC 5-1000), average progno-

sis (WCC 10-30,000) and intensive therapy (WCC 30,000) groups.

TREATMENT MODALITY AND PROTOCOL OUTLINE: Good and average prognosis induced with vincristine and prednisolone, but cytosine and asparaginase are added in average prognosis groups. Intensive therapy group induced with cytosine cyclophosphamide and asparaginase. All children given prophylactic skull irradiation (2400r) and 4 injections of intrathecal methotrexate. Remission is confirmed by bone marrow aspiration. All patients are then randomized into either group A - 6 weeks of chemotherapy consisting of 6MP daily, weekly methotrexate and monthly vincristine followed by 2 weeks of no treatment; or group - some chemotherapy but one week after its cessation 0.25ml of BCG is inoculated with a Heaf gun. (BCG Commonwealth Serum Laboratory Pasteur strain protein content 75mg/ml viable organisms 6-20 x 10 to the 6th power/mg).

PRESENT STATUS: Ninety-seven randomized with at least 3/12 of follow up; 52 pending analysis. 63% C.R. at 152 weeks. No significant difference in BCG arm (48 patients) vs. no BCG arm (49 patients).

### 164. PROTOCOL TMC-1 FOR NON-T ALL IN CHILDREN (AGED 2-14 YEARS)

*Shetty, P. A., Antia, P. K., Damle, S. R., Nadkarni, J. S., Nadkarni, K. S.,* Tata Memorial Hospital, Dept. of Chemotherapy, *Dr. Ernest Borges Marg, Parel, Bombay 400012, Maharashtra, India*

OBJECTIVE: The study is planned to evaluate the importance of reinforcement therapy (same as induction therapy), given once in 3 months, in overall relapse-free survival.

APPROACH: The induction phase and sanctuary phase of treatment are similar for all patients. When the patients reach maintenance phase, they are randomized into two arms: (1) Reinforcement therapy plus maintenance and 2) maintenance therapy alone.

PROGRESS: So far 10 patients have been entered into arm 1 and 7 patients into arm 2. The median duration of follow-up is 6 months. No definite conclusions have been drawn.

### 165. EVALUATION OF INTENSIFICATION AND MAINTENANCE PROGRAMS IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

*Pavlovsky, S., Sackmann Muriel, F.,* Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

DESCRIPTION: A comparative Phase III trial designed to evaluate the usefulness of more frequent pulse of therapy during maintenance. Patients with acute lymphoblastic leukemia (ALL) are randomly assigned to receive pulse at 1, 2, 3, 4 and 6 and every 3 months therafter of: (1) vincristine and prednisone, or (2) sequential pulse with vincristine and prednisone or arabinosyl cytosine and cyclophosphamide successively.

This protocol was opened to all members of the group in January 1976. By June 1978 a total of 250 patients had been entered into this protocol, of whom 241 were evaluable. The results of induction treatment were as follows: 175 (86%) out of 203 children and 31 (82%) out of 38 adults achieved complete remission. According to the WBC count, of those children and adults who had at diagnosis a WBC count lower than 20,000, 91% and 89% achieved complete remission as compared to 75% and 75% of those with more than 20.000 WBC count (43%). From the group with sequential pulses at 18 months 90% and 40% respectively remain in complete remission. There is no statistical difference according to maintenance therapy; however, a highly significant difference (P less than 0.005) was observed according to the WBC count lower or higher than 20,000 in adults and children.

### 166. RANDOMIZED STUDY OF HYPERTRANSFUSION IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

*Ekert, H., Smith, P. J., Toogood, I.,* Royal Children's Hospital, Clinical Haematol & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVES: To determine whether moderate hypertransfusion (Hemoglobin 14-18gm%) can reduce duration of neutropenia and severity of infections in ALL and to study the mechanisms of this protective effect.

APPROACH: Paired randomization has been adopted. All children receive identical chemotherapy. Blood investigations are performed 2 times a week; bone marrow culture in soft agar performed on Day 14; erythropoietin levels to be assayed in both groups of patients.

PROGRESS: Preliminary findings (Lancet I, 776, 1976) show that there was a significantly greater polymorphonuclear count on Day 10 in hypertransfusion group; significantly diminished incidence of infections; and significant reduction in interruptions to chemotherapy. Randomization of 12 pairs of children with ALL confirms these findings. Bone marrow culture has not yet been performed in sufficient numbers of patients to permit evaluation.

Randomized study (Lancet) shows significantly greater polymorphonuclear counts on Days 7 and 10 in hypertransfused group; reduction in incidence of infection and interruptions to chemotherapy. Bone marrow studies suggest that 'stem cell competition' may be the mechanism of action.

### 167. HIGH DOSE METHOTREXATE PROJECT IN LEUKEMIA - DIAGNOSTIC AND THERAPEUTIC STUDIES

*Moe, P. J., Nygaard, R., Dahl, T.,* University of Trondheim, Barneklinikken, *7000 Trondheim, Norway*

I. High dose methotrexate studies.

OBJECTIVE: Our program for treating children with ALL is not followed by all departments of pediatrics in Norway. Different types of biochemical studies are performed on samples from the children in order to classify the cases with respect to type of leukemia and to follow them with respect to activity of the disease.

APPROACH: All children with ALL are receiving a special leukemia treatment program. Clinical and hematological information is obtained on all cases. Lysozyme activity and ferritin concentration are determined before and during therapy of the children. We are also planning other types of studies in order to disclose early relapse, for instance CNS leukemia. Methotrexate determinations are performed in serum and spinal fluid during high dose methotrexate infusion. We are also planning to perform animal studies with tissue analyses of methotrexate.

PROGRESS: Several articles have already been published, among them 1) Pharmacokinetics of high dose methotrexate treatment of leukemia in children, Europ. J. Pharmacology 1978; 2) High dose methotrexate in acute childhood leukemia, Acta Paediatr. Scand., May 1978; 3) Serum lysozyme in children with acute leukemia, Europ. J. Pharmacol, 1978.

II. Childhood leukemia in the Nordic countries. This is an extensive epidemiologic study, involving registration of all long time survivors of acute leukemia in the five Nordic countries.

### 168. PLASMA METHOTREXATE ASSAYS IN ROUTINE TREATMENT FOR ACUTE LYMPHOCYTIC LEUKAEMIA

*Marks, V., Aherne, G. W., Piall, E.,* University of Surrey, Dept. of Biochemistry, *Guildford GU2 5XH, England, United Kingdom*

OBJECTIVE; The reason why some children with ALL relapse, and others on the same regime do not, is obscure but one possibility is that absorption, plasma concentration and persistence of methotrexate are important variables. Certainly there is a great variation in both the frequency and quality of toxic effects encountered. It is proposed to measure plasma methotrexate levels following a standard oral dose in children with ALL in the MRC UK ALL v trial. Analysis of the results may indicate any correlation with toxic effects of methotrexate and with duration of remission.

APPROACH: Five blood samples taken over 5 hours following an oral dose of methotrexate will be collected after 6 months, 18 months and 2 1/2 years of treatment of ALL. The methotrexate concentration in the plasma will be measured by radioimmunoassay at the University of Surrey.

PROGRESS: In the course of studying a small number of patients (23) with ALL two groups of patients were distinguished. In one group the absorption of methotrexate following an oral dose was rapid and in the other - delayed. Patients in the 'slow absorption' group had significantly more drug after a longer period of time than those in the 'fast absorption' group. To date, another 150 series of plasma samples have been assayed but an analysis of the results has not yet been carried out.

## 169. CNS PROPHYLAXIS IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

*Freeman, A. I.*, Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

Fifty percent of children with acute lymphocytic leukemia (ALL) may now be 'cured.' However, CNS impairments are occurring in these long-term survivors. It is not clear whether these problems are secondary to the disease, or to the mode of CNS trial prophylaxis. Cancer and Leukemia Group B (CALGB) in three separate clinical trials (CLB Protocols No. 7111, No. 7411 and No. 7611) has compared cranial irradiation (RT) plus intrathecal (IT) methotrexate (MTX) with IT MTX alone. In an earlier study (CLB Protocol No. 6801) a comparison of IT MTX with no specific CNS prophylaxis was made. We have the unique capability of retrospectively evaluating the effect of CNS prophylaxis on large numbers of randomly treated patients. A pilot study to Protocol No. 761, conducted at Roswell Park Memorial Institue, also tested IT MTX.

We will employ standardized neurological tests, standardized psychological and psychometric tests, CAT scans, EEG's and endocrine evaluation. There will be central review of these tests with evaluators blinded to the CNS treatment regimen received. This study will be a retrospective analysis where patients will be evaluated with the test battery on one occasion (Protocols No. 6801, No. 7111, No. 7411, No. 7611 and No. 7611 - pilot study).

Approximately 150 disease-free children with ALL will be available for study for a two-year period. If both types of CNS prophylaxis are equally effective (i.e., cranial RT plus IT MTX versus intermediate dose MTX plus IT MTX), and one type results in a higher percentage of psychosocial and neurological sequelae, then this information is relevant to future trials and to recommendations for treatment in the community.

## 170. PHASE I STUDY OF 5-AZA-2'-DEOXYCYTIDINE IN CHILDREN WITH LEUKEMIA

*Rivard, G. E., Momparler, R. L.*, St. Justine Hospital, Centre de Recherche Pediatrique, *3175 St. Catherine Rd., Montreal, Quebec*, H3T 1C5, Canada

There is need for new and more effective chemotherapeutic agents in the treatment of acute lymphoblastic leukemias that have become resistant to conventional drugs and for acute non-lymphoblastic leukmia, a disease that responds poorly to chemotherapy. Since 5-AZA-CdR is related to 5-a-acytidine, a drug that has already been shown to be clinically effective in acute leukemia of childhood, and since preliminary data indicate that 5-AZA-CdR is a potent antileukemic agent in animal and possibly in children, the potential usefulness of this agent should be investigated. Using an integrated approach where biochemical, cellular, animal and human studies are performed in the same institution by the same group, the antileukemic potential of 5-AZA-CdR can be rapidly evaluated and if this agent shows great potential, its introduction into a controlled Clinical Phase II study can be accelerated. Also, studying the mechanism of action of 5-AZA-CdR at the biochemical and cellular level with a variety of human leukemic cells and correlating those data with clinical evolution of patients will provide the rationale for the design of the most optimal dose schedules in possible future combination chemotherapy studies.

## 171. LEUKEMIA PROGRAM PROJECT

*Simone, J. V.*, St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The ultimate objective of this program is to cure children suffering from leukemia. The program is a coordinated effort of therapy and study which includes therapeutic trials aimed at prolonging leukemia-free survival with the more efficient use of conventional agents and the development of new agents, studies of the biology and pathogenesis of leukemia and studies of the effects of leukemia and its therapy on normal tissues.

The program consists of seven interrelated projects: (1) Primary therapy of acute lymphocytic leukemia. (2) Primary therapy of acute non-lymphocytic leukemia. (3) Therapy of relapse of leukemia. (4) Leukemia cell kinetics. (5) Studies of in vitro growth of normal and leukemic marrow. (6) Pathogenesis and therapy of pneumonia. (7) Pathogenesis of pancytopenia in mice.

All projects have the same ultimate objective and, though a wide variety of disciplines are involved, the organization structure provides the means for a unified, coordinated effort.

BIBLIOGRAPHIC REFERENCES: Aur, R.J.A., Simone, J.V., Verzosa, M.S., Hustu, H.O., Barker, L.F., Pinkel, D.P., Rivera, G., Dahl, G.V., Wood, A., Stagner, S., and Mason, C.: Childhood acute lymphocytic leukemia. Study VIII. Cancer 42:2123-2134, 1978. George, S.L., Aur, R.J.A., Mauer, A.M., and Simone, J.V.: A reappraisal of the results of stopping therapy in childhood leukemia. NEMB 300: 269-273, 1979.

## 172. BONE MARROW TRANSPLANTATION IN CHILDREN WITH LEUKEMIA

*Dooren, L. J., Vossen, J. M., Rothbarth, P., de Koning, J., Kamphuis, R. P., Rumke, H.*, Academisch Ziekenhuis Leyden, Dept. of Pediatrics, *Rijnsburgerweg 10, 2333 AA Leyden, Netherlands*

OBJECTIVE: Prospective investigation of the results of treatment of children with acute leukemia with poor prognosis in first remission by the transplantation of bone marrow cells from MHC identical sibling donors in comparison with the results of treatment by conventional cytostatic therapy.

APPROACH: Selection of treatment group of high risk leukemia patients, in particular children with acute nn-lymphocytic leukemia. 2. Optimalization of cell reductive and transplantation treatment. 3. Prevention and treatment of complications, optimalization of supportive care, including psychosocial guidance. 4. Detailed longitudinal follow-up of humoral and cellular immune capacities following bone marrow transplantation.

PROGRESS: The project was started in September 1980.

## 173. HYPERTRANSFUSION IN ACUTE MYELOID LEUKEMIA

*Ekert, H., Toogood, I. R., Waters, K. D.*, Royal Children's Hospital, Dept. of Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVE: To investigate the effect of hypertransfusion on the proliferative activities of myeloblasts.

PROJECT: Children with AML and a white cell count below 50,000 will be hypertransfused to a Hb. of 16-18 g/dl prior to commencing chemotherapy. Bone marrow aspirations will be performed before, and 96 hours after, hypertransfusion. Bone marrow morphology, cellularity, labelling indices and culture characteristics will be determined.

PROGRESS: Ten patients have so far been investigated. In 6, hypertransfusion has resulted in a significant increase in L.I. to cells which, morphologically and by culture, appear to be myeloblasts. Patients with an increase in L.I. after hypertransfusion have come into remission. Patients without an increase in L.I. after hypertransfusion have not remitted.

## 174. CLINICAL PROTOCOL (PHASE II) OF REMISSION INDUCTION IN CHILDHOOD ACUTE MYELOBLASTIC LEUKAEMIA (AML)

*Ekert, H., Waters, K. D.*, Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

HISTOLOGIC TYPE AND CLINICAL STAGE: All children with morphologic and cytochemical evidence of AML.

TREATMENT MODALITIES AND AGENTS: Cytosine arabinoside 10 mg/kg is infused over 24 hours. This is followed immediately by daunorubicin 45 mg/m2 and 24 hours later by adriamycin 45 mg/m2. A second course is repeated in 2 weeks. Bone marrow aspiration is used to test remission. All patients continue with cytosine arabinoside and 6-thioguanine for 3 courses at 5 day intervals followed by 5 days of oral cyclophosphamide and 2 further injections of adriamycin 45 mg/m2. Remission is maintained with cytosine and 6-thioguanine and intermittent BCG (Heaf gun inoculation) and allogenic AML cells injected intradermally.

PROTOCOL: Not controlled or randomized.

PRESENT STATUS: 20 entered. 66% C.R.

## 175. ADRIAMYCIN PHARMACOKINETICS IN CHILDREN

*Evans, W. E., Pratt, C. B., Hayes, A., George, S. L., Beck, W. T.*, St. Jude Children's Research Hospital, Clinical Pharmacokinetics Laboratory, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The principal goals of the proposed research are to determine the pharmacokinetic parameters of adriamycin disposition in children with cancer and the relationship of drug disposition to tumor response. Among specific questions that will be asked are the following: (1) Are there significant interpatient and intrapatient differences in the disposition of adriamycin in children? (2) Do the rate of drug metabolism and the extent of drug distribution significantly influence tumor response in children with neuroblastoma? (3) Does patient age, sex, disease status, concurrent drug therapy and/or nutritional status have a predictable influence on adriamycin disposition in children with cancer?

The pharmacokinetics of adriamycin and metabolites will be determined from plasma and urine concentrations determined by HPLC-fluorescence and characterized by a multicompartment physiologic pharmacokinetic model. Distribution characteristics will be further evaluated from serial bone marrow samples obtained before and after adriamycin administration. Tumor response will be measured by changes in the cell kinetics (Labeling Index, Mitotic Index) and flow cytometry of tumor cells obtained from serial bone marrow samples before and after adriamycin administration in children with disseminated neuroblastoma and acute non-lymphocytic leukemia. Previous studies have established the correlation between cell kinetic changes and clinical response in neuroblastoma. Patient variables such as age, sex, concurrent drug therapy, disease status and nutritional status will also be evaluated for their influence on adriamycin disposition.

The above study will provide information on the influence of adriamycin metabolism and/or distribution on tumor response in children with neuroblastoma. It may also provide us with a more rational basis for dosage escalation or chemotherapeutic changes in children that fail to respond to current therapy.

### 176. CLINICAL EVALUATION OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN PEDIATRIC ONCOLOGY

*Wagner, H. P., Baumgartner, C., Bucher, U., Imbach, P.,* Universitat Bern, University Hospitals, Dept. of Pediatrics, *c/o Tiefenauspital, 3004 Bern, Switzerland*

High-dose VAC-type chemotherapy (CT) followed by total body irradiation (TBI), 600 rads, and reimplantation of cryopreserved, autologous bone marrow (0.5 x 10 to the fifth power CFU-c per kg body weight, or more) will be used for the treatment of children with relapsing, advanced Ewing's sarcoma, neuroblastoma, non-Hodgkin's lymphoma, yolk sac tumor or leukemia.

Based on the results obtained, an attempt will be made to define indications for an early use of the aforementioned procedures in the treatment of children with cancer known to have a poor prognosis. As of November 1980, 13 children have received cryopreserved autologous bone marrow after CT and TBI. Time of observation has been too short for evaluation.

### 177. STUDY AND TREATMENT OF CANCER IN THE YOUNG

*Levine, A. S., Poplack, D. G., Glaubiger, D., Pizzo, P. A., Deisseroth, A. B., Magrath, I. T., Simon, R., Ziegler, J. L., Rosenberg, S. A., Glatstein, E., Chabner, B.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Pediatric Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Acute leukemia, non-Hodgkin's lymphomas (e.g., Burkitt's), neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma and aplastic anemia are studied. In the treatment of leukemia, we have devised therapeutic regimens which may allow maximum tumor cell kill while minimizing sequellae. Emphasis is on tailoring treatment to individual prognostic variables, and improving the therapeutic ratio in CNS prophylaxis. In treating the solid tumors, we have developed combined modality approaches to primary disease. In refractory tumors, we are studying the utility of high-dose-therapy and the role of supportive care (platelet and white cell transfusion, laminar-flow protection, autologous bone marrow rescue, total parenterai nutrition) in permitting such therapy. Phase I-II trials are also conducted in refractory tumors; agents include ICRF-187, poly I:C/poly-l-lysine, dihydroxyanthracenedione, and 2'-deoxycoformycin. We are exploring the biology of selected tumors, including kinetics, immunology, virology, tumor markers, genetics, biochemistry, and pharmacology. Also studied are the effects of cancer and its treatment on growth, development, and organ function. The psychosocial concomitants of cancer are explored.

BIBLIOGRAPHIC REFERENCES: Glaubiger, D., Makuch, R., Schwarz, J., Levine, A.S., and Johnson, R.E.: Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. Cancer 45: 2213-2219, 1980. Shackney, S.E., Bunn, P.A., Ford, S.S., Erickson, B., Ross, W.E., and Levine, A.S.: A study of drug-induced kinetic perturbations in the marrow of a patient with neuroblastoma. Cancer 45: 882-892, 1980.

### 178. IMMUNIZATION WITH A VARICELLA-ZOSTER VIRUS VACCINE

*Brunell, P. A., Sumaya, C. V., Grose, C. E.,* University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Pediatrics, *7703 Floyd Curl Dr., San Antonio, Texas,* 78284, United States of America

A live varicella vaccine will be given to children with leukemia. The immune response clinical reactivity and propensity of the vaccine virus to spread to contacts of vaccinees will be evaluated. Responses will be correlated with the immune status, stage of disease and stage of chemotherapy of the vaccine recipient. The objective will be to determine whether children with leukemia can be protected against varicella by immunization without producing significant morbidity with the vaccine. An attempt will be made to determine the host factors which are associated with optimal immune response and minimal morbidity. The goal is to protect children with leukemia against varicella by immunization with live vaccine.

### 179. CHEMOTHERAPY OF ACUTE LEUKEMIA AND RELATED DISORDERS

*Kyle, R. A., Burgert, E. O., Gilchrist, G. S., Smithson, W. A., Hoagland, H. C., Greipp, P. R., Cupps, R. E., Soule, E. H.,* Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

A prospective, randomized study involving chemotherapy of acute leukemia, multiple myeloma, malignant lymphoma and solid tumors is being included in the cooperative activities of Cancer and Leukemia Group B.

BIBLIOGRAPHIC REFERENCES: Kyle, R.A., Gailani, S., Seligman, B.R., Blom, J., McIntyre, O.R., Pajak, T.F., and Holland, J.F.: Multiple myeloma resistant to melphalan: Treatment with cyclophosphamide, prednisone, and BCNU. Cancer Treat. Rep., 63:1265-1269, 1979. Harris, R.B., Perry, H.O., Kyle, R.A., and Winkelmann, R.K.: Treatment of scleromyxedema with melphalan. Arch. Dermatol., 115:295-299, 1979.

### 180. AUTOLOGOUS MARROW TRANSPLANTATION

*Buckner, D., Thomas, E. D., Stewart, P., Bensinger, W.,* Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

We propose to evaluate the effectiveness of high dose chemoradiotherapy in a variety of malignant diseases including acute leukemia, chronic granulocytic leukemia, oat cell carcinoma, malignant lymphoma, ovarian carcinoma, breast carcinoma and resistant pediatric solid tumors. Patients will have marrow cryopreserved prior to therapy and reinfused following intensive therapy with regimens developed in the syngeneic and allogeneic transplant programs. The effectiveness of this approach in terms of marrow repopulation and therapeutic effectiveness will be evaluated.

### 181. HEMOSTATIC DEFECT IN ACUTE LEUKEMIA AND DISSEMINATED SOLID TUMORS (HUMAN)

*Steuber, C. P.,* Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 182. CHILDHOOD ALL

*Falletta, J.,* Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 183. TREATMENT OF LEUKEMIA

*Hathaway, W. E.*, University of Colorado, Health Sciences Center, School of Medicine, Dept. of Pediatrics, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 184. CHEMOTHERAPY OF CHILDHOOD LEUKEMIA AND SOLID TUMORS - ACUTE LYMPHOBLASTIC LEUKEMIA

*Kung, F. H.*, University of California, San Diego Campus, School of Medicine, Dept. of Medicine, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 185. SW ONCOLOGY GROUP - CHEMOTHERAPY OF CHILDHOOD ACUTE LEUKEMIA AND SOLID CA

*Vietti, T. J.*, Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 186. EVALUATION OF TWO MAINTENANCE PROGRAMS FOR CHILDHOOD NON-HODGKIN'S LYMPHOMA WITHOUT PREVIOUS TREATMENT (ABBREV)

*Pavlovsky, S., Bonesana, A. C.*, Grupo Argentino de Tratamiento de la Leucemia Aguda, *P. de Melo 3081, 1425 Buenos Aires, Argentina*

OBJECTIVES: 1. Compare, with an historic control (Protocol 6-LRS-73), whether the adding of adriamycin and cyclophosphamide to vincristine and prednisone in a sequential form and the extension of vincristine administration to 8 weeks increases the percentage of complete remissions, the duration of same and the survival. 2. Evaluate whether preventive treatment of the CNS with intrathecal (IT) methotrexate alone is as effective as prevention with cobalt 60 to the cranium and IT methotrexate. 3. Continue with the two treatment groups of maintenance COPP (lymphoma type) or 6-mercaptopurine, methotrexate, cyclophosphamide (leukemia type) to evaluate their influence on duration of complete remission.

METHODS: Induction (common to all the patients): VCR 1.5 mg/sqm iv days 1, 8, 15, 21, 29, 36, 43 and 50; PRED 40 mg/sqm/day orally days 1 to 14, 22 to 35 and 52 to 61; CTX 600 mg/sqm iv days 1 and 15; ADR 45 mg/sqm iv days 1, 22 and 43. Radiotherapy 3500 rads in the more bulky lymph node areas for 4 weeks; MTX 12 mg/sqm IT days 1, 22, 36, and 43; DM 1 mg/sqm IT days 1,22, 36 and 43. Maintenance: Randomization: Arm I: Combination chemotherapy with: CTX 600 mg/sqm iv days 1 and 8; VCR 1.4 mg/sqm iv days 1 and 8; PCB 100 mg/sqm/day po for 10 days; PRED 40 mg/sqm/day po during 14 days on the first and fifth cycle. Arm II: Combination chemotherapy with: 6MP 2.5 mg/kg/day po; MTX 15 mg/sqm/week po or im; CTX 300 mg/sqm/week orally. Every 3 months reinforcement courses with: VCR 1.5 mg/sqm iv day 1; PRED 40 mg/sqm po days 1 to 7.

PROGRESS REPORT: By June 1978 25 patients had been entered to the protocol, of whom 20 were evaluable and 18 (90%) achieved complete remission. Seven (100%) out of 7 stage I and II and 11 (85%) out of 13 with stage III and IV achieved complete remission. Three out of 6 from Arm I relapsed compared to 3 out of 12 from Arm II.

### 187. PROTOCOL FOR TREATMENT OF HODGKIN'S DISEASE IN CHILDREN

*Lobo, J. F., Garcia, I., Jimenez, E., Camacho, A., Jimenez, B. R., Camacho, M. A.*, Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: 1) To evaluate children with previously untreated Hodgkin's disease, and, based on the clinical stage IA-IIIA (without laparotomy), assign them to two different therapeutic modalities: chemotherapy alone or chemotherapy plus radiotherapy. 2) To evaluate the use of radiotherapy exclusively restricted to invaded areas. 3) To determine the usefulness of cyclophosphamide, vinblastine, prednisone and procarbazine (CVPP) in 28-day cycles for a total of 6 cycles. 4) To determine the usefulness of CVPP plus adriamycin, onocovin and bleomycin (CAVOBPP) without radiotherapy in induction of remission and, then, in maintenance in children with stage IIIB and IV Hodgkin's disease.

PROGRESS: To date 11 patients have been accepted to the protocol. Six have completed treatment and have been in remission 7-18 months. Five are still undergoing treatment.

This protocol is undertaken in coooperation with the Grupo Latinoamericano de Tratamiento de Hemopatias Malignas (GLATHEM-79). (Translated)

### 188. PEDIATRIC ONCOLOGY - HODGKIN'S DISEASE

*Tan, C. T.*, Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 189. STUDY OF VALUE OF CLINICAL AND HISTOLOGIC STAGING AND A PHASE III STUDY OF CHEMOTHERAPY OF HISTIOCYTOSIS X IN CHILDHOOD

*Ekert, H., Waters, K., Smith, P. J.*, Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

The summary for this project is under entry no. 135.

## B. THERAPY OF INTRACRANIAL TUMORS, NEUROBLASTOMA AND NEPHROBLASTOMA

### 190. THERAPEUTIC CONTROLLED STUDY OF PEDIATRIC GLIOMAS

*Ambrosio, A., Colangelo, M., Palmieri, A., Catalano, E., Capece, W., Licenziati, F.*, Ospedali Riuniti per Bambini di Napoli, Dept. of Pediatric Neurosurgery, *Via Mario Fiore 8, 80131 Naples, Italy*

The main goal of the research consists of determining differences between two different combined treatments of the gliomas (Surgery plus Radiotherapy plus Chemotherapy versus Radiotherapy plus Surgery plus Chemotherapy). The evaluation will be made in terms of survival and a useful recovery.

Furthermore, the administration of radiation therapy and of chemotherapy, according to the usual dosages, will be critically estimated by studying their incidence on these parameters: Intracranial pressure (ICP), bioelectrical cerebral activity (EEG), and reduction in the volume of neoplasm.

In the case of pre-surgical irradiation, the approach is performed through the pre-operative evaluation, consisting of CT-scan, monitoring of ICP and EEG, followed by intraoperative observation of a certain number of facors, which are: 1) reduction in the volume of neoplasm, 2) reduction in the bleeding and a much easier hemostasis, 3) a much easier condition for removing the neoplasm from the surrounding area, and 4) a much easier fragmentation of the tumoral mass.

In the case of post-operative irradiation, the approach is made during the follow-up time and it employs the described procedure of evaluation (CT-scan, ICP and EEG monitoring) according to a scheduled program.

### 191. SURVIVAL PROGNOSIS - RADIATION THERAPY FOR BRAIN TUMORS (CHILDREN)

*Danoff, B.*, Thomas Jefferson University, Jefferson Medical College, Dept. of Radiation Therapy & Nuclear Medicine, *1025 Walnut St., Philadelphia, Pennsylvania*, 19107, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 192. INTENSIVE CHEMOTHERAPY AND IMMUNOTHERAPY IN NEUROBLASTOMA STAGES III AND IV - PHASE II STUDY

*Waters, K. D., Ekert, H.*, Royal Children's Hospital Research Foundation, Dept. of Hematology, *Flemington Rd., Melbourne, Victoria 3052, Australia*

HISTOLOGIC TYPE AND CLINICAL STAGE: Neuroblastoma - All paediatric patients with stage III and stage IV neuroblastoma are eligible for study.

TREATMENT MODALITIES: Vincristine, Cyclophosphamide, Adriamycin and Imidazole Carboxamide (DTIC). Transfer factor prepared from one of the parents if tumor immunity can be demonstrated in the parents using a migration inhibitor factor (MIF) assay.

PROTOCOL OUTLINE: The trial will open to all patients with stage III and stage IV neuroblastoma, who have not received any previous chemotherapy. The chemotherapy will be given as follows - Vincristine 1.5mg/m2 IV on days 1 and 5, Cyclophosphamide 600mg/m2 IV on day 1, Adriamycin 30mg/m2 IV on day 3, DTIC 200mg/m2 IV n days 1 to 5. This regimen will be repeated every 29 days. When remission is achieved transfer factor will be given on day 22 of each cycle. Observations during study will be - symptoms and physical findings, documenting size of main lesion; urine catecholamines every eight weeks until normal, than every twelve weeks; skeletal survey every eight weeks till clear, then every twelve weeks; bone marrow aspiration every 8 weeks (if positive initially) until negative, then as indicated clinically. MIF assays to assess anti-tumor immunity will be performed every 12 weeks in the patients treated with transfer factor to document any alterations in tumor immunity. Patients with progressive disease will be removed from study. Patients showing a partial response or static disease will remain on study until progressive disease occurs. Patients who demonstrate a complete response will remain on therapy for 24 months.

PROGRESS: Twenty patients entered on study, 13 patients died, 7 alive. Median survival time - 22 months. Study will continue, and it is planned to enter 4 or 5 patients per year.

### 193. PROTOCOL OF TREATMENT FOR NEUROBLASTOMAS USING SURGERY, RADIOTHERAPY, CHEMOTHERAPY - PHASE III

*Lobo, J. F., Garcia, I., Vargas, G., Camacho, M. A., Carrillo, H. J., Jimenez, B. R., Jimenez, E., Navarrete, M., Mora, L.*, Hospital Nacional de Ninos, Dept. of Onco/Hematologia, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To improve survival through therapeutic approach in relation to age and extent of disease.

APPROACH: Under 1 year: Stages I and II: resection and chemotherapy; Stages III and IV: chemotherapy (vincristine, cyclophosphamide, adriamycin). Over 1 year: Stages I and II: resection, chemotherapy, radiotherapy. Stage III: chemotherapy, radiotherapy with 60Co. Stage IV: chemotherapy. Controlled trial.

PROGRESS: Twenty-five cases under study. (Translated)

### 194. PREVENTION AND REVERSAL OF MALNUTRITION IN NEUROBLASTOMA

*Baehner, R. L., Rickard, K. A., Grosfeld, J. L., Matchett, N., Weetman, R. M., Provisor, A. J., Boxer, L. A., Oei, T. O.*, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Pediatrics, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

The prognosis for stage IV children with neuroblastoma is dismal. Aggressive multimodal treatment programs often result in severe malnutrition (PEM) which interferes with therapy and increases morbidity and mortality. The plan of this study is to evaluate the effectiveness of enteral and parenteral nutrition in preventing and/or reversing PEM, maintaining or restoring immune competence, preventing treatment delays, and improving tumor response of 36 children (ages one to six years) with metastatic neuroblastoma receiving chemotherapy (5 drugs: Cytoxan, vincristine, DTIC, adriamycin, VM-26) every three weeks. At diagnosis, children who are considered nourished at diagnosis will be randomized to receive either a comprehensive enteral nutrition program or total parenteral nutrition (TPN) for the first 35 days of treatment. Children considered malnourished at diagnosis will be randomized to receive either TPN or partial parenteral nutrition plus enteral nutrition for the first 35 days of the treatment. Thereafter, all children will receive a comprehensive enteral nutrition program. Nutritional status, recall skin test response, treatment delays and tumor response will be evaluated at 0, 6, 12, 18 and 22 weeks. Additional nutritional evaluations (dietary, anthropometric and biochemical) will be determined weekly during the first 5 weeks to identify nutritional indices of clinical and subclinical PEM in children undergoing treatment for metastatic neuroblastoma.

### 195. STUDY AND TREATMENT OF CANCER IN THE YOUNG

*Levine, A. S., Poplack, D. G., Glaubiger, D., Pizzo, P. A., Deisseroth, A. B., Magrath, I. T., Simon, R., Ziegler, J. L., Rosenberg, S. A., Glatstein, E., Chabner, B.*, U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Pediatric Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The summary for this project is under entry no. 177.

### 196. CLINICAL EVALUATION OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN PEDIATRIC ONCOLOGY

*Wagner, H. P., Baumgartner, C., Bucher, U., Imbach, P.*, Universitat Bern, University Hospitals, Dept. of Pediatrics, *c/o Tiefenauspital, 3004 Bern, Switzerland*

The summary for this project is under entry no. 176.

### 197. PHASE I AND II DRUG TESTING PROGRAMS

*Rivera, G.*, St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 198. ADRIAMYCIN PHARMACOKINETICS IN CHILDREN

*Evans, W. E., Pratt, C. B., Hayes, A., George, S. L., Beck, W. T.*, St. Jude Children's Research Hospital, Clinical Pharmacokinetics Laboratory, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The summary for this project is under entry no. 175.

### 199. PROTOCOL OF TREATMENT FOR NEPHROBLASTOMAS USING SURGERY, RADIOTHERAPY AND CHEMOTHERAPY - PHASE III

*Lobo, J. F., Garcia, I., Piza, E. J., Camacho, M. A., Jimenez, E., Jimenez, B. R.*, Hospital Nacional de Ninos, Dept. of Onco/Hematologia, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To establish value of 3 modes of treatment in relation to stage of tumor.

APPROACH: Histologic-surgical evaluation of degree of invasion, study of metastases and classification by stages. Use of actinomycin-D and vincristine at stage I; addition of radiotherapy with 60Co at stage II and III; and adriamycin at stage III and IV. (Controlled trial.)

PROGRESS: Twenty-five patients under study - 2 deaths. (Translated)

### 200. NEPHROBLASTOMA - ADJUVANT CHEMOTHERAPY

*Fossati Bellani, F., Domini, R.*, Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

A therapeutic protocol for nephroblastoma is now in progress and a national study is being organized.

### 201. THE USE OF A FOUR-DRUG COMBINATION CHEMOTHERAPY REGIME (DAVE) IN THE TREATMENT OF ADVANCED WILMS' TUMOR

*Malpas, J. S., Graham Pole, J. R., Dunger, D. B.*, Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A four-drug combination using dactinomycin, adriamycin, vincristine and endoxan (cyclophosphamide) together with surgery and irradiation was used in the treatment of stage III and stage IV Wilms' tumor with undifferentiated histology. Eighty percent of children in the study group achieved a complete response. Of these children who achieved a complete response the median survival time has not yet been reached, but must be in excess of 3 1/2 years. Toxicity has not been a problem with the drug combination used. Histology and site of metastases have been important prognostic factors.

### 202. NATIONAL WILMS' TUMOR STUDY

*D'Angio, G. J., Evans, A. E., Breslow, N., Beckwith, J. B., Tefft, M.*, American Academy of Pediatrics, *1801 Hinman Ave., Evanston, Illinois*, 60204, United States of America

Modern treatment methods have led to a major improvement in the survival rate of children with Wilms' tumor. Combined therapy using surgery, radiation therapy, and chemotherapy now cures more than 85% of patients. However, the outlook is poor for those with unfavorable histology and metastases at diagnosis (about 50% survival). More effective means of treating these patients must be developed. At the same time, all treatments have their risks and complications, and refinements of therapy for those with a good prognosis are needed so as to achieve maximum surivval with the least morbidity. NWTS-1 is now complete, and its primary and secondary objectives have been achieved. 'Natural history' and epidemiologic information has been reported. Gross and microscopic features associated with an unfavorable outlook have been identified. Combined therapy using actinomycin-D (AMD) and vincristine (VCR) is superior to the use of either agent alone. Routine radiation therapy (RT) is not needed in all children with early stage disease. Review of RT given children with more advanced stages, however, left to be defined its role in the modern management of these patients. NWTS-2 is now in the stage of data analysis. Preliminary results suggest that 6 months of AMD and VCR maintenance therapy is satisfactory for Group I children, none of whom receives RT, and that the addition of adriamycin to AMD and VCR gives better results than the use of the two latter alone. NWTS-3 will build on the first two studies and use the staging system developed therefrom. Studies are presently planned to seek answers to the following questions: (1) Is two months of AMD and VCR maintenance therapy enough for Stage I? (2) Is RT needed for Stage II? (3) Does 1000 rad suffice for the treatment of Stage III? (4) Can a better drug regimen be devised for Stage IV and unfavorable histology? (5) What are the late adversities of successful treatment in NWTS patients?

### 203. NUTRITION SUPPORT OF CHILDREN WITH WILMS' TUMORS

*Rickard, K. A., Baehner, R. L., Grosfeld, J. L.*, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Nutrition & Dietetics, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

The early diagnosis and multimodal treatment of children with Wilms' tumors have vastly improved survival rates. However, severe malnutrition (PEM) and numerous complications and toxicity are often associated with the treatment. Malnutrition reduces the capacity to withstand aggressive treatment, increases susceptibility to opportunistic infections, depresses immune function and increases morbidity and mortality. The purpose of this study is to prospectively evaluate the benefits and complications of several modes of nutrition support (i.e., enteral nutrition, partial parenteral nutrition - PPN, peripheral nutrient infusion with enteral nutrition - and total parenteral nutrition - TPN, central nutrient infusion) in children (ages one to seven years) receiving multimodal treatment for Wilms' tumors, stages II-IV. Each regimen will be evaluated for its effectiveness in preventing or reversing PEM, maintaining or restoring immune competence, and obviating treatment modifications and complications. Children with stage II-IV Wilms' tumors who are considered malnourished at diagnosis will be randomized to receive either TPN or PPN throughout the period of irradiation. Nourished children with either stage IV or stage II/III and unfavorable histology Wilms' tumors will be randomized to receive either PPN or TPN throughout the six weeks of abdominal irradiation. Nourished children with stage II/III and favorable histology Wilms' tumors will receive either a comprehensive enteral nutrition program or PPN throughout the four weeks of intense treatment which includes abdominal irradiation. Thereafter, all children will receive a comprehensive enteral nutrition program to prevent subclinical PEM during 2, 3, or 4 drug chemotherapy maintenance programs. Nutritional state, immunological capacity, treatment modifications and complications will be evaluated at diagnosis and at 4, 6, 19, and 26 weeks during the initial, intense and maintenance periods.

### 204. STUDIES OF CHILDHOOD SOLID TUMORS

*Simone, J. V., Pratt, C. B., Green, A., Mauer, A. M., Hustu, H. O., Hayes, A., Kumar, M., Beck, W., George, S., Rivera, G., Evans, W., Nakajima, F.*, St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The overall objective of this project is to develop a coordinated effort to improve the results of treatment of children with solid tumors. This goal is to be achieved through the systematic development of specific treatment regimens for primary care of children with solid tumors as well as for the testing of new agents in Phase I and Phase II studies. In addition, there will be an attempt to develop an epidemiological approach to the children with cancer seen at St. Jude Hospital and also to develop a pharmacological approach to the altered drug pharmacokinetics in children with cancer. The goals set for the current year, the second in this project, are: 1) To develop a multidisciplinary approach to the treatment and evaluation of children with neuroblastoma. 2) To develop a multidisciplinary treatment program for children with osteosarcoma. 3) To plan and initiate an epidemiological program involving the solid tumor patients at St. Jude Hospital with special reference to the unusual occurrence of adenocarcinoma of the colon in childhood and adolescence in this region. 4) To investigate in animal systems and later in children with solid tumors the mechanism by which biotransformation of drugs is altered in experimental neoplasms and the relationship of this effect to polyamines. 5) To study the biological activity of new anticancer chemotherapeutic drugs in children with solid tumors using Phase I and Phase II type testing programs.

## C. THERAPY OF RETINOBLASTOMA, RHABDOMYOSARCOMA AND OTHER SOLID TUMORS

### 205. PROTOCOL OF TREATMENT FOR RETINOBLASTOMA USING SURGERY, RADIOTHERAPY AND CHEMOTHERAPY - PHASE III

*Lobo, J. F., Guerrero, L. J., Piza, E. J., Camacho, M. A.*, Hospital Nacional de Ninos, *Apdo. 1654, San Jose, Costa Rica*

OBJECTIVE: To establish the usefulness of treatment comprised of surgery, radiotherapy and chemotherapy according to stage of tumor.

APPROACH: Determination of stage: Stage 1 - surgery; Stage 2 -chemotherapy for 1 year (vincristine plus cyclophosphamide), surgery; Stage 3 - surgery, radiotherapy and chemotherapy using vincristine, cyclophosphamide, methotrexate; Stage 4 - same as 3 plus radiotherapy to metastases. Controlled trial.

PROGRESS: Twenty-five patients under evaluation. (Translated)

### 206. CONSERVATIVE SURGERY, RADIOTHERAPY AND CHEMOTHERAPY IN TREATMENT OF EMBRYONIC RHABDOMYOSARCOMA

*Rodriguez, C., Gomez, J., Martinez, L. C., Rodriguez, H., Gutierrez, R., Forero, E.*, Instituto Nacional de Cancerologia, Seccion de Cirugia, *Apartado Aereo #17.158, Calle 1 No. 9-85, Bogota, DE, Colombia*

OBJECTIVE: To evaluate the results of conservative surgery, radiotherapy and chemotherapy in the treatment of embryonic rhabdomyosarcoma; specifically, in the treatment of patients over 16 years of age with confirmed diagnosis of embryonic rhabdomyosarcoma.

MATERIAL AND METHODS: Conservative surgery is considered to be intervention which does not compromise the function of a limb, and if that were to be the case, it would be limited to biopsy or partial resection. Radiotherapy is administered at conventional dosages pre-established by protocols of treatment for other malignant soft-tissue tumors. Chemotherapy is administered according to the schema Vincristine/Actinomycin-D/Cyclophosphamide (VAC) at dosages established by protocols on norms and procedures. It is administered over 2 years. (Translated)

**207. NATIONAL CANCER PROGRAM FOR CHILDREN**

*Bozek, J., Czerwinski, W., Perek, D., Ordyniec, J.,* National Research Inst. for Mother & Child, Clinical Department of Child Oncology, *17 Kasprzaka Str., 01211 Warsaw, Poland*

OBJECTIVE: Optimization of the methods of treatment of rhabdomyosarcoma in children. Actual results of the treatment of rhabdomyosarcoma in children are far from satisfactory. Depending on staging, the relapse-free survivals (RFS) are 0-15 percent for 5 years. This results from the biological nature of the tumor and late diagnosis.

APPROACH: Advances in diagnosis of rhabdomyosarcoma and optimization of methods of therapy including radiotherapy, chemotherapy and surgery have to be made on the basis of centralized material from all the medical centers in our country.

PROGRESS: Progress is expected to be achieved in a) centralization of the treatment area, b) generalization of modern methods of diagnosis, and c) the best mode of treatment used in all of the cases registered and diagnosed in a centralized clinical area.

**208. PEDIATRIC ONCOLOGY - EMBRYONAL RHABDOMYOSARCOMA**

*Ghavimi, F.,* Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

**209. STUDY AND TREATMENT OF CANCER IN THE YOUNG**

*Levine, A. S., Poplack, D. G., Glaubiger, D., Pizzo, P. A., Deisseroth, A. B., Magrath, I. T., Simon, R., Ziegler, J. L., Rosenberg, S. A., Glatstein, E., Chabner, B.,* U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Pediatric Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The summary for this project is under entry no. 177.

**210. PEDIATRIC ONCOLOGY - EWING'S SARCOMA**

*Rosen, G.,* Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

**211. PEDIATRIC ONCOLOGY - OSTEOGENIC SARCOMA**

*Rosen, G.,* Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

**212. CLINICAL EVALUATION OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN PEDIATRIC ONCOLOGY**

*Wagner, H. P., Baumgartner, C., Bucher, U., Imbach, P.,* Universitat Bern, University Hospitals, Dept. of Pediatrics, *c/o Tiefenauspital, 3004 Bern, Switzerland*

The summary for this project is under entry no. 176.

**213. STUDIES OF CHILDHOOD SOLID TUMORS**

*Simone, J. V., Pratt, C. B., Green, A., Mauer, A. M., Hustu, H. O., Hayes, A., Kumar, M., Beck, W., George, S., Rivera, G., Evans, W., Nakajima, F.,* St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

The summary for this project is under entry no. 204.

**214. HUMAN LEUKOCYTE TREATMENT OF PATIENTS WITH VARIOUS MALIGNANT DISEASES**

*Strander, H., Nilsonne, U.,* Karolinska Sjukhuset, *S10401 Stockholm, Sweden*

Continuation of the clinical trial of interferon treatment for osteosarcoma: Patients admitted to the Karolinska Hospital since 1971 are all receiving interferon. Prognostic factors, metastases and survival compared to a concurrent control group consisting of all the other cases of osteosarcoma treated in Sweden during the same time. At present the frequency of metastases is about 50 percent in the interferon treated group as compared to the control group. A similar difference is obtained as regards survival.

A pilot study is done on juvenile laryngeal papilloma where patients exhibiting progressing tumor growth are treated with interferon. Regression has been demonstrated in 7 so treated cases. Upon removal of interferon progression again occurred. Regression has again been demonstrated after resumption of interferon administration.

Myeloma pilot study: Interferon has been shown to cause regression of multiple myeloma, even complete remissions. A pilot study is now continuing including also melphalan resistant myeloma cases.

A randomized study on multiple myeloma has been initiated where interferon therapy is compared to conventional melphalan-prednisolone treatment.

Studies of the effect of interferon therapy on malignant melanoma and ovarian cancer are to be initiated.

**215. THERAPY OF PAPILLOMATOSIS OF RESPIRATORY TRACT (HUMAN)**

*Turtz, M.,* St. Christopher's Hospital for Children, *2600 N. Lawrence St., Philadelphia, Pennsylvania,* 19133, United States of America

This is part of a broader project. A summary of this subproject is not available.

**216. CARCINOMA OF THE COLON IN CHILDHOOD AND ADOLESCENCE**

*Pratt, C. B.,* St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

This is part of a broader project. A summary of this subproject is not available.

## D. PHARMACOKINETICS, THERAPEUTIC COMPLICATIONS AND PATIENT SUPPORTIVE CARE

**217. INFECTIOUS COMPLICATIONS IN CHILDHOOD LEUKEMIA - A RETROSPECTIVE AND PROSPECTIVE STUDY**

*Lahde, P., Vesikari, T.,* Tampere Yliopisto, Inst. of Clinical Sciences, *Pl 607, 33101 Tampere 10, Finland*

Infectious complications in patients under 15 years of age with leukemia or lymphoma treated in Tampere Central Hospital between 1963 and 1979 are being reviewed. The information is being applied for more effective specimen collection and laboratory studies in the prospective part of the study. New patients entering the study are being screened for immunity against various viruses and protozoa. In addition to studies on acute infections, the occurrence of latent cytomegalovirus infection will be followed in the patients by repeated serological testing of CMV early antigen-antibody and by virus isolation. At the same time the patients are being studied for cell-mediated immunity by lymphocyte stimulation and skin testing.

**218. THERAPY-INDUCED GROWTH DISORDERS IN CHILDHOOD CANCER**

*Duck, S. C., Camitta, B. M., Klitgaard, H., Drucker, W. D., Hagen, T. C., Guansing, A. R.,* Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin,* 53233, United States of America

Acute lymphocytic leukemia (ALL) is the most common malignancy of childhood. Currently about 50% of children diagnosed as having ALL will survive for 5 or more years. With improved survival times, many serious adverse effects of cancer therapy are being manifested: some of these are leucoencephalopathy, disrupted growth and development and neuroendocrine dysfunction. At present it is uncertain whether one can predict which children will experience these particular adverse effects and what if anything can be done to prevent expression of hormone dysfunction. The specific objectives are: 1. To establish if at any stage of therapy for ALL, there is an impairment of the neuroendocrine-endocrine end-organ axis, and to what extent such impairment is exposed clinically by disturbed growth and development. 2. To establish the relative 'necessity'

and 'potential benefit' of appropriately timed trials of exogenous hormone therapy based on the temporal characteristics of these endocrine disruptions. Methods will involve a four-year prospective evaluation of newly diagnosed children with ALL. The new patients will be enrolled during the first 2 years of the study, allowing 2-3 year follow-up for the survivors. Each patient will be evaluated by extensive, sequential anthropometric parameters, bone age analyses, and basal and 'stress'-released hormone levels, measured at each phase of cancer therapy.

BIBLIOGRAPHIC REFERENCES: Duck, S.C., Drucker W.D.: Cortisol response to ACTH1-24 and insulin-induced hypoglycemia in children treated for acute leukemia. The Endocrine Society (Washington, D.C.), 1980, in press.

**219. LATE EFFECTS OF PEDIATRIC CANCER THERAPY - EMERGENCE OF 6-TG VARIANT LYMPHOCYTES**

*Lange, B. J.*, Children's Hospital of Philadelphia, Joseph Stokes Jr. Research Institute, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

OBJECTIVE: The ultimate objective of this project is to investigate the potential mutagenic effects of regimens used to treat pediatric cancer patients. The immediate objective is to determine the frequency of 6-TG-resistant peripheral blood lymphocytes emerging before, during and after combination therapy and to characterize the 6-TG-resistant population.

APPROACH: We use the short-term autoradiographic method of Strauss and Albertini (Mutat. Res. 61:353, 1979) which measures variant frequency by inhibition of 3H thymidine incorporation in PHA-stimulated lymphocytes in the presence or absence of 2 times 10 to the minus 4th power M 6-TG.

PROGRESS: We have studied longitudinally or prospectively 80 samples in 50 healthy children or adults and 80 specimens in 62 patients with Hodgkin's disease or sarcomas before, during and after chemotherapy and irradiation. We have confirmed that some cancer patients have increased numbers of 6-TG-resistant lymphocytes before therapy. Both irradiation and chemotherapy further increase the numbers of detectable variant cells, especially in Hodgkin's disease. The increased frequency disappears in sarcoma patients during therapy or once it is stopped; it persists in some Hodgkin's disease patients. We are developing 6-TG-resistant cell lines to characterize the mechanism of 6-TG resistance.

**220. EPIDEMIOLOGY AND LATE EFFECTS OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN**

*Whitaker, J. N., Ochs, J., Simone, J. V.*, U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1030 Jefferson Ave., Memphis, Tennessee*, 38104, United States of America

The objective of this research project is to determine if the measurement of myelin basic protein in cerebrospinal fluid will have predictive or monitoring value for the central nervous system involvement in acute lymphoblastic leukemia or the side effects from treatment of this disease. The plan is to obtain serial cerebrospinal fluid specimens from patients entering different therapeutic protocols for the treatment of acute lymphoblastic leukemia. The cerebrospinal fluid will be coded and analyzed as to basic protein peptide 43-88 concentration by a double antibody radioimmunoassay. The immunoassay requires extensive use of a refrigerated centrifuge and a gamma counter. This study has just been initiated and information is too preliminary to form any conclusion. For this investigation only patients at St. Jude Children's Research Hospital will be studied. Their cerebrospinal fluid will be analyzed in the Laboratory of Neurobiology at the Memphis VA Medical Center.

**221. CHANGES IN ACUTE LYMPHOCYTIC LEUKEMIA LYMPHOBLASTS CAUSED BY INDUCTION CHEMOTHERAPEUTIC AGENTS IN VIVO**

*Wells, R. J.*, University of North Carolina, Chapel Hill Campus, School of Medicine, Dept. of Pediatrics, *Manning Dr., Chapel Hill, North Carolina*, 27514, United States of America

OBJECTVE: Determine the changes which occur in acute lymphocytic leukemic lymphoblast metabolism when these cells are exposed to induction chemotherapeutic agents in vivo.

APPROACH: Serial samples of lymphoblasts will be obtained from the peripheral blood of children with acute lymphocytic leukemia prior to and during induction chemotherapy. Lymphoblast glucocorticoid receptors, cell viability, size, uptake of radiolabeled glucose, nucleotides and amino acid and cell RNA, DNA and protein content will be measured.

**222. EFFECTS OF CNS TREATMENT ON INTELLECTUAL FUNCTIONING OF CHILDREN WITH LEUKEMIA**

*Moss, H. A., Poplack, D. G., Hubbard, V. S.*, U.S. Dept. of Health & Human Services, Public Health Service, Alcohol, Drug Abuse & Mental Health Admin., National Inst. of Mental Health, Developmental Psychology Laboratory, *Bethesda, Maryland*, 20014, United States of America

The effects of CNS treatment (cranial irradiation and intrathecal chemotherapy) on the cognitive and perceptual functioning of children with leukemia are investigated. One study compared a group of leukemic children in remission with a matched group of sibs. Comparisons were based on results from a battery of psychological tests (Wechsler, Bender-Gestalt and Graham-Kendall) administered to the children. These groups are followed-up 12-15 months after the initial assessment. A sample of leukemia patients who have not received CNS treatment and their sibs and a sample of cystic fibrosis patients and their sibs are also being assessed using these procedures to control for effects other than CNS treatment. A second study deals with another sample studied prospectively. In this instance children in remission from leukemia are evaluated on the same battery of psychological tests as in the first study. They are tested just prior to prophylactic CNS treatment and are re-evaluated one year later to determine if any possible brain changes brought on by the CNS treatment have resulted in learning disabilities and diminished intellectual functioning. The healthy siblings of the leukemics receiving CNS treatment, who are being studied retrospectively, will be used as a control group to check testing effects.

**223. NEUROPSYCHOLOGICAL EFFECTS OF LEUKEMIA AND ITS TREATMENT**

*Berg, R. A.*, St. Jude Children's Research Hospital, Dept. of Psychiatry/Psychology/Social Services, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee*, 38101, United States of America

The proposed study will investigate the neuropsychological status of children treated for acute lymphoblastic leukemia (ALL) in a longitudinal fashion by means of serial neuropsychological, audiological, and electroencephalographic examinations and by comparison with control groups consisting of siblings of leukemic children and comparably aged children with Wilms' tumor. All children admitted to St. Jude Children's Research Hospital for treatment of ALL between the ages of four and twelve (40-50 per year) will be serially evaluated for five years by means of the Reitan-Indiana Neuropsychological Test Battery for Children or the Halstead Neuropsychological Test Battery for Children as well as by electroencephalograms and the Staggered Spondeic Word Test. Identical procedures will be administered to the control groups. If alterations in neuropsychological functioning do occur, they are expected to be variable across age groups, consistent within age groups. A thorough statistical analysis of the data will result in the detection of areas of neuropsychological dysfunction and determination of the etiology of any dysfunctions which occur. The determination of specific areas of neuropsychological dysfunction will facilitate the development of remediation strategies applicable to the classroom. Academic achievement will be monitored yearly to assess the effectiveness of any remediation initiated. By thoroughly examining a population at risk of developing CNS dysfunction during the high risk period, new knowledge can be obtained not only concerning the population of ALL children but also concerning the developing CNS in general.

**224. OCCULT DISEASE IN ACUTE LEUKEMIA BEFORE CHEMOTHERAPY DISCONTINUANCE (HUMAN)**

*Mahoney, D. H.*, Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

This is part of a broader project. A summary of this subproject is not available.

**225. PAIN AND ANXIETY IN CHILDREN WITH ACUTE LEUKEMIA**

*Kellerman, J.*, Children's Hospital of Los Angeles, Dept. of Pediatrics, *4650 Sunset Blvd., Los Angeles, California,* 90054, United States of America

This study was designed to evaluate the efficacy of training in hypnosis in reducing pain and anxiety in children with acute lymphoblastic leukemia (ALL) undergoing bone marrow aspirations (BMA's). Patients/subjects were selected from the population of children between the ages of 6 and 10 years of age with ALL, receiving outpatient treatment in the Division of Hematology-Oncology at Children's Hospital of Los Angeles. The design calls for randomization of 40 patients to either hypnosis or attention/placebo groups, with stratification of the sample by sex. Baseline measures are collected along four dimensions: behavioral observation, nurse ratings, and structured self-ratings of pain and anxiety. Two training sessions are offered post-baseline and prior to the next outpatient bone marrow aspiration. Further sessions are provided prior to each of three post-baseline bone marrow aspirations and response to training is monitored using the four dependent measures. Seventeen patients accrued to the study in Year 1, 9 in the hypnosis group, 8 in the comparison group. Baseline data was collected on all patients. Fourteen of 17 patients have completed 2 sessions of introductory training (7 each in both hypnosis and comparison groups). Twelve patients have undergone at least one post-training bone marrow aspiration (6 each in both groups). Of these, 4 patients (three patients in the hypnosis group and one patient in comparison group) have undergone 2 BMA's, and 2 patients (one each, in both groups) have completed the study protocol and have gone off-study (three post-training BMA's). Two methodological modifications were made. Hypnotic susceptibility testing was not done because the major pediatric susceptibility scales were, essentially, hypnotic inductions. Exposing comparison group patients to hypnotic induction would have confounded the controlled nature of the study. A quantified rating of the child's response to either hypnosis or the attention/placebo dimension was added as a factor to be correlated with treatment efficacy. All data were coded prospectively.

**226. PSYCHOLOGICAL AND SOCIAL CONSEQUENCES OF CHILDHOOD LEUKEMIA**

*Maguire, G. P., Comaroff, J., Morris Jones, P.*, Withington Hospital, Dept. of Psychiatry, *West Didsbury, Manchester M2O 8LR, England, United Kingdom*

OBJECTIVES: 1. To determine the incidence of psychological and social problems in parents of children who are being treated for leukemia in the first 12 months after diagnosis. 2. To compare this with the incidence of such problems in parents with healthy children. 3. To determine the factors that determine which parents develop psychological and social problems.

APPROACH: Systematic semistructured interviews with each patient in the home shortly after diagnosis and 12 months later. Each interview is tape-recorded to allow independent checking and coding.

PROGRESS: The project is nearing completion. The results indicate that serious problems can develop and the provision of counselling could do much to help parents adjust to the disease and its treatments.

**227. CHILDHOOD CANCER - PSYCHOSOCIAL REHABILITATION**

*Lansky, S. B., Cairns, N. U., Butterfield, G.*, University of Kansas, Medical Center, School of Medicine, Dept. of Pediatrics, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

In the third year of the current granting period, we will complete accrual of patients and analysis of data in the following three areas of study: 1. Patient compliance with oral chemotherapy and psychological factors associated with noncompliance. 2. The costs of childhood cancer, both medical and nonmedical. 3. The intellectual and academic status of children with cancer with particular attention to those who receive prophylactic central nervous system treatment (irradiation and/or chemotherapy).

BIBLIOGRAPHIC REFERENCES: Lansky, S.B., Vats, T., and Cairns, N.U. Refusal of treatment, a new dilemma for oncologists. Amer. J. Ped. Hematology/Oncology, 1, 277-282, 1979. Cairns, N.U., and Lansky, S.B. MMPI indicators of stress and marital discord among parents of children with chronic illness. Death Education, 4, 29-42, 1980, in press.

**228. BEHAVIORAL STUDIES OF SERIOUSLY ILL CHILDREN**

*Susman, E. J., Strope, B. E., Hersh, S. P., Levine, A. S., Pizzo, P. A.*, U.S. Dept. of Health & Human Services, Public Health Service, Alcohol, Drug Abuse & Mental Health Admin., National Inst. of Mental Health, Developmental Psychology Laboratory, *Bethesda, Maryland,* 20014, United States of America

Physical well-being is an assumed, though generally unmeasured, condition in studies of the child's psychological development and behavior. There is little developmental inquiry concerning the effects of absence or loss of physical well-being on child development, despite the reality that acute or chronic ill health from disease or accident is, to a great or small degree, part of the life of every child. This project is concerned with the psychological and social impact of serious illness (cancer) on children and those in their social network (namely their families and caregivers). Areas of research include coping abilities, the influence of the social system of the child, and the mutual influences of the stressed children and those in their social network. Observations, interviews, and parent and nurse ratings were used to investigate these phenomena.

BIBLIOGRAPHIC REFERENCES: Susman, E.J., Hollenbeck, A.H., Nannis, E.D., and Strope, B.E. A Developmental Perspective on Psychosocial Aspects of Childhood Cancer. In Schulman, J.L., and Kupst, M.J. (Eds.): The Child with Cancer -Clinical Approaches to Psychosocial Care. Springfield, Illinois, Charles C. Thomas, 1980, pp. 129-142.

**229. PEDIATRIC ONCOLOGY - A STUDY OF FAMILY NEEDS**

*Malpas, J. S., Clark, J. A.*, Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

This study into the effects of calamitous disease on the relatives of children with cancer has been an in-depth inquiry into the problems of families. It has been carried out using questionnaires and interviews in a representative cross-section of patients under the care of the unit. Problems of nurse communication and liaison (hospital sister to community nurse), the special problem of fathers, of adolescents and of the bereaved are under investigation.

**230. COPING IN FAMILIES WITH A LEUKEMIC CHILD**

*Schulman, J. L., Kupst, M. J.*, Children's Memorial Hospital, Division of Child Psychiatry, *707 W. Fullerton St., Chicago, Illinois,* 60614, United States of America

Ninety-three families of children with leukemia and meningitis have been seen as part of the Coping Project, a five-year longitudinal study. Objectives are: 1) To obtain multi-source and multi-method data on the coping behaviors of family members; 2) to determine the relationship of coping and variables thought to be related to healthy coping; and 3) to test the effectiveness of an intervention strategy that is intended to help families maximize their coping resources and deal effectively with the illness and its implications.

Families were assigned randomly to one of three groups: 1) Total intervention; 2) moderate intervention; or 3) no coping project intervention. A series of clinical interviews has been conducted with the family: at diagnosis, during hospitalization, at home visits, in the outpatient phase, final assessments. Families are also asked to complete a number of scales, including the CPI, the Current Adjustment Rating Scale, and the Missouri Children's Picture Series. Tapes of the interviews are rated by psychosocial staff using the Hurwitz, Kaplan and Kaiser scale, which has been adapted for use in this setting, and the Borgatta Interaction Process Analysis. Physicians and nurses also complete ratings of the families, based on the Coping scale and the Mood and Behavior scale. Systematic observations of behavior during the inpatient stays and in the clinic have been done, using time-sampling of child and adult behavior.

The current year, which is the fifth and last year of the project, will be spent in compiling the data, analyzing them, and presenting the results.

## 231. MANAGEMENT OF CHILDHOOD LEUKEMIA AS A FAMILY CRISIS

*Fife, B. L., McAdoo, W. G., Groom, G. L.*, Indiana University - Purdue University at Indianapolis, School of Nursing, Dept. of Nursing Services, *1232 W. Michigan St., Indianapolis, Indiana,* 46202, United States of America

This project is divided into two phases. Phase One will be a baseline study that will measure the specific effects of the stress of childhood leukemia on family life in terms of marital adjustment, school behavior of the patient and siblings, the quality of family functioning, and the level of anxiety of individual family members. These data will then be used to develop an intervention plan which will be tested in Phase Two of the study to determine if such a program is effective in helping families deal with the stress of childhood leukemia in such a way that the development of secondary psychosocial problems is minimized. Phase Two will make use of an experimental design with a treatment and a control group, and the same outcome measures will be used for both phases of the project.

## 232. ADJUSTMENT AND ADAPTATION IN CHILDREN WITH CANCER

*Spinetta, J. J., Kung, F. H., Schwartz, D. B., Hartman, G.*, California State University & Colleges, San Diego State University, School of Sciences, Dept. of Psychology, *5402 College Ave., San Diego, California,* 92115, United States of America

The major objectives of the proposed continuation project are: (1) To continue into a fourth and fifth year to test for the presence of trends in psychosocial reaction of the child to cancer and its treatment; (2) to catalog sibling behaviors relative to the cancer and its treatment, both during the course of the illness and after the child's death; and (3) to test specific methods for the reduction of emotional, social, and/or academic dysfunctioning in the child with cancer which may result from the illness and its treatment, so that the child can continue to participate as fully and successfully as possible in family, community, and regular school life.

The testing for the presence of possible trends will come from a continued careful and methodic assessment of the child (attitudinal and behavioral components) in response to his environment (personal, familial, and situational). The project will encompass a continued extensive longitudinal series of assessments of the children in each age level, in varying circumstances (hospital, out-patient clinic, home and school). Stress will be placed on behavioral elements in day-to-day issues, and both behavioral and attitudinal variables at critical illness points. The study will attempt to differentiate healthy from unhealthy coping responses in the child.

The testing of methods for the reduction of dysfunctioning will be by specific interventions geared to expressed problems on an individual child and family basis. Central problems to be studied are: (1) Methods for the reduction of treatment-associated pain, (2) methods for the reduction of school-related problem behaviors, and (3) methods for the reduction of faulty intra-family and child-staff communication.

BIBLIOGRAPHIC REFERENCES: Spinetta, J.J. Communication patterns in families dealing with life-threatening illness. In O.J.Z. Sahler (ed.), The child and death. St. Louis: C.V. Mosby, 1978. Spinetta, J.J. Coping with childhood cancer: Professional and family communication patterns. In M. Eisenberg (ed.). Communication in the health care setting. Springfield, IL: C.C. Thomas, 1979, in press.

## 233. DEMONSTRATION UNIT FOR ADOLESCENT CANCER PATIENTS

*Wallace, H. J.*, Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

A ten-bed inpatient demonstration unit for adolescent cancer patients has been in operation since January 5, 1978 at RPMI. The Unit is designed to provide special rehabilitation and support personnel and facilities to minimize the impediments to accomplishing the tasks of adolescence when these are complicated by cancer and its treatment. The specially selected and trained staff has cared for eighty-seven teenage and young adult patients with a broad variety of cancers in the first eight months of operation. Primary nursing has made the nurse a more integral part of the patient management team and more cognizant of the patient, disease, treatment and family concerns. The nurse's role is expanding as the greater demands of primary nursing are met.

A primary goal of the Unit is to provide strong psychosocial support for the patients, families and staff. A number of programs and activities have been developed to meet this goal based on a baseline study of adolescent cancer patient needs. Activities include patient rap sessions, occupational therapy, family night, music therapy, creative writing, concerts/movies and bereavement follow-up. Documentation of the programs has been accomplished and evaluation data have been collected. Analysis and comparison with a prior study is under way. The Unit will be the focus of numerous research projects, some of which are already under way.

## 234. PEDIATRIC CANCER CONTROL - SCHOOL AND NURSING OUTREACH

*Cairns, N. U., Klopovich, P., Trueworthy, R., Suenram, D., Butterfield, G.*, University of Kansas, Medical Center, School of Medicine, Dept. of Pediatrics/Psychiatry, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

With advances in therapy, childhood cancer has become a chronic disease which need not prevent a child from living a normal or near-normal life much of the time. The purpose of the proposed project is to develop and evaluate a model for utilizing two existing community resources, the school and the county health department, to facilitate the child's rehabilitation. Community health nurses educated in pediatric cancer care can alleviate many of the burdens on children and families living at a distance from the treatment center. School, a major force in normal child development, is as important in children's rehabilitation as employment is for the adult cancer patient.

A Pediatric Cancer Control Team (PCCT) has been formed consisting of two pediatric oncology nurse clinicians, two clinical psychologists, a special education teacher, and support personnel. The objectives are, first, to educate local community health nurses and school personnel about pediatric cancer, cancer therapy, prognosis, and rehabilitation; second, to maintain liaison with the local agencies to coordinate medical care and to facilitate academic progress for each patient; and third, to evaluate the effectiveness of the program by means of (a) questionnaires to assess local community personnel's knowledge about and attitudes toward cancer both before and after intervention; (b) weekly patient contact logs to provide information about the community nurse's activities; (c) school records of the child's attendance and academic progress; and (d) parent questionnaires and interviews to assess satisfaction with the intervention. To date, 41 children are involved in the study.

## 235. PUBLIC POLICIES AFFECTING CHRONICALLY ILL CHILDREN AND THEIR FAMILIES

*Hobbs, N., Perrin, J. M., Ireys, H. T., Roberts, F. B., Hauck, R. J., Shayne, M. W., Moroney, R. M., Pless, I. B.*, Vanderbilt University, School of Medicine, Dept. of Psychology/Preventive Medicine & Public Health, *21st Ave. S. & Garland, Nashville, Tennessee,* 37232, United States of America

The purpose of this study is to develop specifications for a national policy responsive to the special needs of chronically ill children and their families. The disease entities to be studied include: juvenile diabetes, cystic fibrosis, muscular dystrophy, spina bifida, sickle-cell anemia, hemophilia, leukemia, childhood autism, severe asthma, and severe heart, lung, and kidney diseases. Approximately 650,000 children are involved. The policies to be studied include several titles of the Social Security Act (principally Title V), the Education for All Handicapped Children Act of 1975, the Rehabilitation Act of 1975, the Rehabilitation Act of 1973 and Amendments of 1978, the Developmentally Disabled and Bill of Rights Act of 1975 and Amendments of 1978, and others, including proposals for a national health insurance program. Private sector insurance programs will also be studied. The study will follow procedures for policy analysis and formulation developed by the Center to guide its work. The procedures call for a definition of the problem in light of existing knowledge, an analysis of existing policies, an identification of major policy options, and the design of implementation and evaluation plans for preferred options. Approximately 40 'State of Knowledge' papers will be commissioned. The study will be guided by an advisory committee, an interagency panel, and a

consortium of investigators. A set of separately funded empirical studies will be carried out.

# V. OTHER CLINICAL STUDIES ON PEDIATRIC NEOPLASMS

## A. COOPERATIVE GROUPS

### 236. FREIBURG COOPERATIVE LEUKEMIA STUDY (1975)

*Wehinger, H.,* Kinderklinik am Stadtkrankenhaus, *Moenchebergstrasse 41, 3500 Kassel, Hessen, Federal Republic of Germany*

OBJECTIVES: To find an optimal two-drug regimen for maintenance in childhood ALL.

APPROACH: This is a cooperative study of several German pediatric departments. Children with ALL who have been successfully brought into remission with vincristine and prednisone are subjected to meningosis prophylaxis, and then randomized to receive: a) 6-MP p.o. daily plus MTX p.o. once weekly; b) 6-MP p.o. daily plus MTX i.v. once every two weeks; or c) 6-MP p.o. daily plus MTX i.v. once every two weeks x4 followed by 6-MP p.o. daily plus Cyclo i.v. once every two weeks x4. The MTX course and the Cyclo course will alternate successively.

PROGRESS: We are still at the stage of patient accumulation.

### 237. NEW ENGLAND PEDIATRIC ONCOLOGY CONSORTIUM

*Forman, E. N., Cornell, C. J., Dickerman, J. D., Truman, J. T.,* Rhode Island Hospital, *593 Eddy St., Providence, Rhode Island,* 02903, United States of America

The overall objective of this protocol is to coordinate and integrate the investigative activities of four New England pediatric oncology centers (Brown University/Rhode Island Hospital, Dartmouth College/Dartmouth-Hitchcock Medical Center - Norris Cotton Cancer Center, Harvard University/Massachusetts General Hospital, University of Vermont/Medical Center Hospital - Vermont Regional Cancer Center) into a single program, the New England Pediatric Oncology Consortium (NEPOC), which, through active membership in the Southwest Oncology Group (SWOG), will effectively contribute to the development of a greater understanding of and more effective treatments for malignancies in children.

Through formalization and efficient organization of cooperative efforts, the most effective use of the resources of each institution will be achieved and will enable full participation and significant input into the activities of SWOG.

### 238. INTERGROUP RHABDOMYOSARCOMA STUDY

*Maurer, H. M., Ruymann, F., Sutow, W. W., Raney, R. B., Lawrence, W., Ragab, A. H.,* Virginia Commonwealth University, Medical College of Virginia, Dept. of Pediatrics, *1200 E. Broad St., Richmond, Virginia,* 23298, United States of America

The Intergroup Rhabdomyosarcoma Study (IRS), a collaborative effort of Children's Cancer Study Group, and Southwest Oncology Group, is a multi-disciplinary study designed to answer important questions about the treatment and biological characteristics of rhabdomyosarcoma in childhood and adolescence. Initiated in November, 1972, IRS-I closed to patient entry in November, 1978, and IRS-II began. Data obtained in IRS-I bear on the surgical, radiotherapeutic, and chemotherapeutic aspects of treatment in relation to disease stage and primary site of tumor origin. Information of prognostic value relative to histology, primary site and sex emerged. Two new histologic subtypes plus patterns of disease spread in relation to primary site, of importance in design of new treatment regimens, have been identified. Two-year disease-free survival rates in IRS-I are 89-90 percent in Group I, 70-75 percent in Group II, 60-65 percent in Group III, and 30 percent in Group IV.

Developed as an outgrowth of IRS-I, IRS-II has as its major goals to further refine treatment in Group I; increase disease-free survival rates in Groups II-IV with prolonged intensive chemotherapy, and more aggressive radiation in Group IV: prevent CNS extension from head and neck sites with radiation and chemotherapy; assess primary chemotherapy vs. primary surgery for GU tumors; develop a pathologic staging classification.

As in IRS-I, IRS-II will be monitored by a multi-disciplinary steering committee composed of surgeons, radiotherapists, chemotherapists, pathologists and biometricians representing the two participating cooperative cancer treatment groups.

BIBLIOGRAPHIC REFERENCES: Raney, R.B., Jr., Gehan, E.A., Maurer, H.M., Newton, W.A., Jr., Ragab, A.H., Ruymann, F.B., Sutow, W.W., and Tefft, M. (For the Intergroup Rhabdomyosarcoma Study Committee). Evaluation of Intensified Chemotherapy in Children with Advanced Rhabdomyosarcoma (Clinical Groups III and IV). Clinical Ca. Trials Spring 1979, p. 19-28.

### 239. INTERGROUP EWING'S SARCOMA STUDY

*Nesbit, M. E., Robison, L., Kissane, J. M., Askin, F. B., Stratton, L. B.,* University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The Intergroup Ewing's Sarcoma Study is a collaborative effort by three national cancer clinical trial groups, Children's Cancer Study Group, Southwest Oncology Group, and Cancer Leukemia Group B, to conduct clinical trials on children and young adults with Ewing's sarcoma of bone. A multi-disciplinary committee composed of chemotherapists, surgeons, radiotherapists, pathologists and statisticians representing the three cooperative groups was organized in 1972 to develop a Phase III clinical trial for previously untreated Ewing's sarcoma. The objectives of the intergroup Ewing's sarcoma studies are to improve the survival of patients with localized and metastatic disease using systematic chemotherapy and radiation therapy.

BIBLIOGRAPHIC REFERENCES: Nesbit, M.E.: Ewing's Sarcoma. Minnesota Medicine, pp. 513-515, July, 1979.

### 240. PEDIATRIC ONCOLOGY GROUP (POG)

*Morgan, S. K.,* Medical University of South Carolina, School of Medicine, Dept. of Pediatrics, *80 Barre St., Charleston, South Carolina,* 29401, United States of America

The proposed research consists of conducting collaborative clinical therapeutic trials according to specific chemotherapeutic, surgical, pathological, and radiotherapy protocols in children with neoplastic disease; reporting the results of these trials; conducting research which may more generally influence the field of oncology; and promoting an educational role demonstrating a multidisciplinary approach to pediatric cancer. This type of approach is primarily directed toward improved patient care, particularly with regards to prolonging or increasing survival and improving the quality of survival. This may be achieved more effectively by cooperative studies among various medical centers so that significant numbers of children with cancer may be evaluated effectively.

### 241. PEDIATRIC ONCOLOGY GROUP - OPERATIONS OFFICE

*Vietti, T. J.,* Washington University, School of Medicine, Dept. of Pediatrics, *660 S. Euclid Ave., St. Louis, Missouri,* 63110, United States of America

On June 8th, 9th and 10th, Dr. Hoogstraten met with the Pediatric Division members in St. Louis. This included the Division's Executive Committee, the chairmen of Pediatric Surgeons, Radiation Therapists, Pathologists and the Principal Investigators from twenty-eight of the thirty-two member institutions. Two major decisions were made: to separate from the Adult Division and form a new Pediatric Group; and to elect Dr. Teresa Vietti as Chairman of the newly formed group. The name will be selected at a later date. A Scientific Support Committee was formed, which will be responsible for the scientific direction of the group. This Committee will report directly to the Group Chairman and the Executive Committee and will interface with all disease committees. It will suggest scientific avenues that need investigation to the disease committees and review proposed protocols for scientific merit. Dr. van Eys has been selected by Dr. Vietti to chair this very important committee, but his appointment is dependent on confirmation by the Executive Committee.

This revised budget was prepared by Dr. Vietti under the advice and guidance of Dr. Hoogstraten. The new Operations Office will be located in St. Louis.

**242. CANCER AND LEUKEMIA GROUP B**

*Holland, J. F., Wasserman, L. R., Cuttner, J., Aufses, A. H.,* City University of New York, Mount Sinai School of Medicine, School of Medicine, Dept. of Neoplastic Diseases, *1 Gustave L. Levy Pl., New York, New York,* 10029, United States of America

OBJECTIVES: A. To participate in the cooperative studies of the various therapeutic regimens in acute leukemia, chronic leukemia, multiple myeloma, the lymphomas, breast cancer, lung cancer, gastrointestinal cancer and other adult solid tumors to be studied by the Cancer and Leukemia Group B. B. The toxicity and therapeutic range of new agents will be determined in Phase I studies; the frequency, extent and duration of remission with new agents will be evaluated in the Phase II studies; and the relative efficacy of various therapeutic regimens at different stages of the disease will be determined in Phase III studies. C. To complete our development into a multidisciplinary group with full participation of surgeons and radiotherapists. This goal has been achieved with the participation of breast surgeons. We plan to extend this participation to general surgeons. D. To develop and participate in studies using immunotherapeutic agents in neoplastic disease states. E. To utilize the case material for the cooperative chemo- and radiotherapy studies for ancillary investigations of some of the biological, biochemical and immunological aspects of the neoplastic diseases under study.

BIBLIOGRAPHIC REFERENCES: Kyle, R.A., Gailani, S., Seligman, B.R., Blom, J., McIntyre, O.R., Pajak, T.F. and Holland, J.F.: Multiple Myeloma Resistant to Melphalan Treatment with Cyclophosphamide, Prednisone and BCNU. Cancer Treat. Rep. 63:1265-1269, 1979. Chahininan, A.P., Mandel, E.M., Holland, J.F., Jaffrey, I.S. and Terstein, A.S.: MACC (methotrexate, adriamycin, cyclophosphamide and CCNU) in Advanced Lung Cancer. Cancer 43: (No. 5) 1590-1597, 1979.

**243. ACUTE LEUKEMIA COOPERATIVE GROUP B**

*Kung, F. H., Nyhan, W. L., Yu, A. L., Byfield, J., Utley, J., Pilch, Y. H., Barone, R., Mendelson, J.,* University of California, San Diego Campus, School of Medicine, Dept. of Pediatrics, *P.O. Box 109, La Jolla, California,* 92093, United States of America

This proposal represents a request to support participation in Cancer and Leukemia Cooperative Group B. This cooperative research is devoted to the investigation of chemotherapeutic approaches to acute leukemia and other human neoplastic diseases. Significant palliation and prolongation of survival has been achieved and contributions have been made in clinical pharmacology. However, the real objective of these studies is the eradication of neoplastic disease by treatment. Studies are being designed to reflect an increasing intensity of attack on the neoplastic cell. The cooperative group technique permits the prompt evaluation in series of reasonable size of promising leads in chemotherapy. These leads or new approaches are often suggested by the results of the group's own work in clinical oncology. Thus, a completed protocol often suggests the new avenues to be explored in new protocols. In addition, protocols are designed to exploit maximally clinical or conceptual advances made in experimental animals. The Division of Hematology-Oncology of the Department of Pediatrics has been a member of Acute Leukemia Group B since 1963. The University of California at San Diego has gradually taken on an interdisciplinary character. Participation of Divisions of Radiation-Oncology, Medicine and Pathology has been active for the past 6 years. Other disciplines including Surgery and Psychiatry are becoming increasingly involved in this work.

**244. CANCER AND LEUKEMIA GROUP B RADIOTHERAPY COMMITTEE**

*Glicksman, A. S., Reinstein, L. E., Tefft, M., McShan, D.,* Rhode Island Hospital, *593 Eddy St., Providence, Rhode Island,* 02903, United States of America

This is a request for supplemental funding so that the Radiotherapy Office of the CALGB through its Quality Assurance Program can undertake the quality assurance of two Pediatric Intergroup Studies, the Intergroup Rhabdomyosarcoma Study-2 and the National Wilm's Tumor Study-3. Dr. Melvin Tefft is the radiotherapy representative of the CALGB to both of these studies and is a member of the CALGB Quality Assurance Overseers Committee. The intent at this time is to utilize the organization, procedures, and overall facilities of the CALGB Quality Assurance Program for the two Intergroup Pediatric Studies rather than to establish free-standing, independent, quality assurance programs for IRS-2 and NWTS-3.

**245. SOUTHWEST ONCOLOGY STUDY GROUP**

*Crist, W. M., Roper, M., Dearth, J. C., Cooper, M. D.,* University of Alabama in Birmingham, School of Medicine, Dept. of Pediatrics, *1919 7th Ave. S., Birmingham, Alabama,* 35233, United States of America

Increased support is requested to permit full participation of the 19 former ALGB, Pediatric Division, members who have recently joined the Pediatric Division of the SWOG to participate in the ongoing immunologic evaluation of pediatric patients with acute lymphocytic leukemia. Specifically, these additional funds will be used to prepare highly purified antibodies to detect cytoplasmic and surface immunoglobulins within or upon lymphoblasts, to obtain other needed supplies as specified, and to support the additional technical personnel required.

**246. MULTIMODALITY THERAPY OF CHILDREN AND ADOLESCENTS**

*Sinks, L. F.,* Georgetown University, School of Medicine, Dept. of Pediatrics, *3800 Reservoir Rd. N.W., Washington, District of Columbia,* 20007, United States of America

This proposal describes the participation of the Division of Pediatric and Adolescent Oncology of the Vincent T. Lombardi Cancer Research Center at Georgetown University in the collaborative efforts of the Southwest Oncology Group (SWOG).

The objective is to facilitate clinical cancer therapy studies, specifically in children and adolescents with neoplasia. The methods used are those of the standard cooperative group procedure.

**247. SOUTHWEST ONCOLOGY GROUP - PEDIATRICS**

*Leventhal, B. G., Kaizer, H., Civin, C. I., Haller, A. J., Wharam, M. D., Zinkham, W., Quddus, F. F.,* Johns Hopkins University, School of Medicine, Dept. of Pediatrics, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

Participation of senior oncology faculty in the Pediatric Oncology Group. It is proposed that the senior faculty will continue their participation in this group with assistance particularly in the design of new protocols for non-lymphocytic leukemia, bone marrow transplantation, double half body in rhabdomyosarcoma and neuroblastoma.

Patient accrual and participation in group protocols will continue at a vigorous level.

The glucocorticoid receptor laboratory, which has been organized and has begun to function, will begin correlation of receptor studies with other clinical features of the leukemia cell studies as measured in other laboratories.

**248. MULTIDISCIPLINARY STUDIES OF CHILDHOOD CANCER - SWOG**

*Maurer, H. M., McWilliams, N. B., Russell, E. C., Dunn, N. L., Hazra, T. A., Lawrence, W., Salzberg, A., Kay, S., Mohanakumar, T., Snead, R. W.,* Virginia Commonwealth University, Medical College of Virginia, Dept. of Pediatrics, *1200 E. Broad St., Richmond, Virginia,* 23298, United States of America

The multidisciplinary team of pediatric oncology investigators at the Medical College of Virginia will: (1) participate collaboratively with Southwest Oncology Group in cooperative programs to determine the optimal treatment regimens for infants, children and adolescents with leukemia and solid tumors; (2) continue to provide leadership in treatment of childhood rhabdomyosarcoma through the Intergroup Rhabdomyosarcoma Study of CALGB, CCSG and SWOG; (3) provide leadership in neuroblastoma and sarcoma studies; (4) develop studies of late effects of cancer therapy in children; (5) develop and participate in SWOG pilot studies in childhood cancer; (6) provide leadership in surface marker and other immunological studies; (7) collect precise data by high quality performance and adherence to protocol procedures and record-keeping; (8) participate in modality and disease-oriented subcommittees of SWOG to develop multidisciplinary studies of therapy for childhood cancer.

BIBLIOGRAPHIC REFERENCES: Maurer, H.M., (for the IRS Committee): The Intergroup Rhabdomyosarcoma Study. II: Objectives and study design. J. Pediatr. Surg. 15:371, 1980. (Maurer, H.M., Chairman IRS Committee), Tefft, M.,

Hays, D., Raney, R.B., Lawrence, W., Soule, E., Donaldson, M.H., Sutow, W.W., Gehan, E.: Radiation to regional nodes for rhabdomyosarcoma of the genitourinary tract in children: Is it necessary? Cancer 45:3066, 1980.

**249. SOUTHWEST ONCOLOGY GROUP STUDIES**

*Vats, T. S., Trueworthy, R., Smith, S., Lansky, S., Cairns, N., Wood, G., Stewart, D., Morantz, R., Neff, J.,* University of Kansas, Medical Center, School of Medicine, Dept. of Pediatrics, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

OBJECTIVES: 1. To participate in the cooperative approach to the design and conduct of clinical trials in malignant diseases. These diseases include leukemia, lymphoma, childhood solid tumors and other neoplasms to be studied by the Southwest Oncology Group. These studies will be classified as Phase I for the evaluation of toxicity, tolerated dosage and therapeutic range of new combinations of agents; Phase II to determine the frequency, extent and duration of remission with new agents; and Phase III to establish the relative efficacy of various therapeutic regimens in neoplastic diseases. Phase I studies will include clinical and experimental pharmacologic investigations such as absorption, plasma half-time, body fluid levels and excretion in man and animal model. 2. To investigate some of the biochemical and biological aspects of the neoplasms under study as they derive from patient material available for the cooperative studies. 3. To actively participate in and continue to contribute to the overall Group effort. This will include scientific input, support in protocol design, chairmanship of studies and other activities called for.

**250. SOUTHWEST ONCOLOGY GROUP STUDIES**

*Hoogstraten, B., Stephens, R., Fabian, C., Park, C., Belt, R., Taylor, S.,* University of Kansas, Medical Center, School of Medicine, Dept. of Medicine, *39th St. & Rainbow Blvd., Kansas City, Kansas,* 66103, United States of America

OBJECTIVES: 1. To participate in the cooperative approach to the design and conduct of clinical trials in malignant diseases. These diseases include leukemia, lymphoma, multiple myeloma, adult solid tumors and other neoplasms to be studied by the Southwest Oncology Group. These studies will be classified as Phase I for the evaluation of toxicity; tolerated dosage and therapeutic range of new combinations of agents; Phase II to determine the frequency, extent and duration of remission with new agents; and Phase III to establish the relative efficacy of various therapeutic regimens in neoplastic diseases. Phase I studies will include clinical and experimental pharmacologic investigations such as absorption, plasma half-time, body fluid levels and excretion in man and animal model. 2. To investigate some of the biochemical and biological aspects of the neoplasms under study as they derive from patient material available for the cooperative studies. 3. To actively participate in and contribute to the overall Group effort. This will include scientific input, support in protocol design, chairmanship of studies and other activities called for.

**251. SOUTHWEST ONCOLOGY GROUP - PEDIATRIC DIVISION**

*Berry, D. H.,* University of Arkansas, Medical Sciences Campus, School of Medicine, Dept. of Pediatrics, *4301 W. Markham St., Little Rock, Arkansas,* 72201, United States of America

The grant proposal objectives are: 1) To implement multidisciplinary clinical research in pediatric oncology. 2) To pursue oncology research by participation in the formulation of protocols for clinical investigation of pediatric oncology diseases and by contribution to data collection, analysis and interpretation for such investigations. 3) To encourage fruitful intellectual exchanges between pediatric specialists in oncology and immunology and foster pilot studies involving these 2 disciplines. 4) To enable SWOG to contribute by intellectual stimulation and information from the group to the education, research and training programs in pediatric oncology at UAMS for all medical and para-medical personnel. The superiority of multimodal rather than single mode therapy in childhood oncology has been well established by SWOG, intergroup studies and other groups. With multidisciplinary research efforts on a local and group basis more complete and better therapies will continue to be developed in pediatric oncology. Since the total number of patients with childhood oncology disease is low, pooling patients in group designed protocols leads to more meaningful randomized studies and rapid collection of data. Assembling oncology investigators with common goals from a number of institutions encourages germination of innovative ideas not easily achieved from a very narrow base. The thoughtful evaluation by many investigators of a proposed protocol prior to its institution leads to more precisely defined questions and makes less likely the omission of pertinent points that can be resolved by adequate data collection.

**252. SOUTHWEST ONCOLOGY GROUP**

*Vietti, T. J., Ternberg, J. L., Perez, C. A., Askin, F. B., Land, V. J., Zarkowsky, H. S., Bell, M. J., Bower, R., Thomas, P., Bergamini, R., Sedlis, M.,* Washington University, School of Medicine, Dept. of Pediatrics, *660 S. Euclid Ave., St. Louis, Missouri,* 63110, United States of America

The Children's Cancer Center at St. Louis Children's Hospital is the larger of only two such centers within a 200 mile radius which offer multimodal therapy to children with malignant disease, regardless of ability of pay. Twenty percent of the 350 patient pediatric oncology census is totally medically indigent and most of the rest can afford to pay only part of the charges.

At the time of diagnosis of a malignancy in a child, the clinical findings are reviewed and management is discussed at the weekly pediatric tumor conference by the pediatric oncologist, radiation therapist, surgeons and pathologists, in order to assure that each child receives optimal therapy. Access to new intensive multimodal therapeutic regimens and experimental compounds is facilitated by the collaboration of the Center with the Southwest Oncology Group of which the Principal Investigator serves as Pediatric Vice-Chairman. The Center will become the home of the Operations Office of the newly formed Pediatric Oncology Group, and the Principal Investigator its Group Chairman, on January 1, 1981.

**253. SOUTHWEST ONCOLOGY GROUP**

*Humphrey, G. B., Nitschke, R., Sexauer, C. L., Blackstock, R., Smith, E. I., Tunell, W. P., Taylor, T. J.,* University of Oklahoma, Health Sciences Center, School of Medicine, Dept. of Pediatrics, *Box 26901, Oklahoma City, Oklahoma,* 73190, United States of America

The Pediatric Division of the Southwest Oncology Group has formally severed its affiliation with the Adult Division of the Southwest Oncology Group and has formed a new international cooperative group of pediatric oncologists. The name chosen for this group was the Pediatric Oncology Group (POG). Dr. Teresa Vietti will be the Chairman of this new group. Active protocols of the Pediatric Division of SWOG will be continued and completed under the POG administration.

Headquarters will be in St. Louis. The Statistical Office will be in Florida under the leadership of Dr. Jon Shuster. Th objectives of POG will be virtually identical to those of the Pediatric Division of SWOG. We wish to effect curative treatment regimens for pediatric malignancies that are currently not curable and reduce the toxicity and duration of treatment where we have curative therapy. We plan to initiate basic science protocols that will allow us to gain new insights into tumor biology, aid in better diagnosis of pediatric malignancies, and evaluate questions in genetics, tumor immunology, etc.

BIBLIOGRAPHIC REFERENCES: Humphrey, G.B., Blackstock, R., Filler, J.: Cell Surface Markers in Acute Lymphoblastic Leukemia. Annals of Clinical and Laboratory Science 10(3):169-180, 1980. Sexauer, C.L., Krous, H.F., Kaplan, R.J., Barnes, P.D., Humphrey, G.B., Supratentorial Primitive Neuroectodermal Tumor: Clinical Response of a Single Case to Vincristine, Cyclophosphamide, and BCNU. Ped. Onc. Vol I, in press, 1980.

**254. SOUTHWEST ONCOLOGY GROUP**

*Falletta, J. M., Metzgar, R., Filston, H. C., Kinney, T. R., Noell, K. T., Fishburn, R. I., VanWezel, G.,* Duke University, School of Medicine, Dept. of Pediatrics, *Box 3711, Durham, North Carolina,* 27710, United States of America

The goal of the proposed research is to determine optimum care for children with all types of cancer. The research mechanism involves participation in collaborative multidisciplinry clinical cancer research protocols generated through the Pediat-

ric Oncology Group (formerly Pediatric Division of the SWOG). The proposed research grant will allow the continued participation of the Divisions of Pediatric Hematology-Oncology, Microbiology and Immunology, Pediatric Surgery, Therapeutic Radiology, and Pathology at Duke University Medical Center in Pediatric Oncology Group activities. These activities involve studies of the natural history, immunology, and multimodal therapy of all childhood malignancies. Cooperative studies among physicians from a group of medical centers allows for rapid accrual of a statistically significant number of children with cancer in order to quickly define those avenues of therapy which provide prolonged disease-free survival. Through participation in cooperative studies, the entire medical community engaged in the care of children with cancer has a focal point to provide not only improved patient care, but also improved multidisciplinary teaching and research. Our objectives for the coming years are: 1) to develop additional protocols for the immunologic diagnosis and management of patients with malignant lymphoproliferative disorders, 2) to continue our multidisciplinary research efforts in other cancers of children, and 3) to expand our outreach programs for education and patient care to satellite institutions and physicians in the regions.

BIBLIOGRAPHIC REFERENCES: Dowell, B.L., Falletta, J.M., Moore, J.O., and Metzgar, R.: Detection and Partial Characterization of Human Thymus-Leukemia Antigens. Journal of NCI 65(4):691-701, October 1980.

### 255. SOUTHWEST ONCOLOGY GROUP PROGRAM

*Talbert, J. L., Donnelly, W., Marcus, R., Mehta, P., Stranfjord, S., Million, R., Walker, D. R., Rodgers, B., Thar, T. L.,* State University System of Florida, University of Florida, School of Medicine, Dept. of Pediatrics/Surgery, *1600 Archer Rd., Box J-266, Gainesville, Florida,* 32610, United States of America

The W.A. Shands Teaching Hospital of the University of Florida serves as the major referral center within a 300-mile radius offering comprehensive, multimodal therapy for children with malignant disease, regardless of their ability to pay. Sixty-six of these pediatric oncology patients are totally medically indigent and the majority of the remainder can afford to pay only a fraction of their treatment costs.

At the time of a malignancy in a child, the clinical findings are reviewed and management discussed at a weekly multidisciplinary Tumor Board conference by pediatric oncologists, radiation therapists, surgeons, pathologists, and other appropriate specialists to ensure that each patient receives optimal therapy. Access to new intensive multimodal therapeutic regimens and experimental compounds is facilitated by the collaboration of the Center with the Southwest Oncology Group.

A variety of ancillary studies, both at the clinical and the preclinical levels are being performed in the Pediatric Oncology patients at the University of Florida in tandem with SWOG protocol investigations. The technique of thoracoscopy has been evaluated and perfected in the surgical laboratory to the point that it now provides major assistance in the diagnosis and management of a variety of pediatric malignancies. Application of the technique of cryosurgery to childhood cancer management is now entering the phase of clinical application, having been assessed initially in animal investigations. Polyamine measurement in blood, urine, bone marrow and cerebrospinal fluid is undergoing evaluation as a marker of disease activity. A Phase I-II clinical trial of vindesine in childhood leukemia has been performed in collaboration with the University of Kansas and a Phase II clinical trial of vindesine is being proposed to the Southwest Oncology Group. The relative effectiveness of various antibiotic regimens in the management of fever and neutropenia in children with malignancy is also undergoing assessment. Finally, protocols are being formulated by members of the U. of F. SWOG program for treatment of metastatic osteosarcoma and histiocytosis X in bone, and for evaluation of the significance of myelofibrosis in ALL.

### 256. SOUTHWEST ONCOLOGY GROUP (CLINICAL)

*Ragab, A. H., Lui, V. K., Kim, T. H., Woodard, J. R., O'Brien, M. S., Whitehead, T., Simmons, G., Alvarado, C., Hawkins, H., Hale, S., Dearing, V.,* Emory University, School of Medicine, Dept. of Pediatrics, *1364 Clifton Rd. N.E., Atlanta, Georgia,* 30322, United States of America

The Pediatric Hematology/Oncology Division at Emory University is the only patient cancer center within a radius of 180 miles. The center offers multimodal therapy to children with malignant disorders. Although this division was inactive for a period of one year, it is currently very active and caring for approximately 300 children with malignant disorders. This division is unique in that it cares for private patients at Emory University Clinic and The Henrietta Egleston Hospital for Children and for indigent patients at Grady Memorial Hospital. This division cares for children in the Atlanta area (population 1.7 million), the State of Georgia, and other neighboring states including North and South Carolina and Alabama. This center is the largest contributor to the pediatric division of POG.

In collaboration with the Pediatric Oncology Group, the center offers access to new intensive therapeutic regimens and experimental agents to approximately 300 children with malignant diseases. An extensive ancillary study, both at the clinical and at the preclinical level, is under way in parallel with the Pediatric Oncology Group studies in children with malignant disorders. Thus, the bone marrow culture technique for the growth of granulopoietic and erythroid progenitor cells is being used to evaluate the effects of chemotherapeutic agents on granulopoiesis and erythropoiesis in man. The same technique is being applied to investigate the cryopreservation of human bone marrow cells and tumor cells. We hope that these studies will offer new insight into the effect of chemotherapeutic agents and the management of children with malignant disorders.

In addition, studies are currently under way to grow childhood tumor cells in culture (Neuroblastoma and Wilms' Tumor). Studies are also under way to investigate the effect of different chemotherapeutic agents on 3 leukemic cell lines.

### 257. SOUTHWEST ONCOLOGY GROUP, PEDIATRIC DIVISION

*Pullen, D. J., Miller, R. C., Hickman, B. T., Johnson, W. W., Iyer, R. V., Jackson, J. F., Routh, A.,* University of Mississippi, Medical Center, School of Medicine, Dept. of Pediatrics, *2500 N. State St., Jackson, Mississippi,* 39216, United States of America

The University of Mississippi Medical Center (U.M.C.) Department of Pediatrics has participated in the treatment protocols and activities of the Southwest Oncology Group (SWOG) since July 1970. In addition to the U.M.C. Division of Pediatric Oncology, the disciplines of pediatric surgery, pediatric pathology and radiation therapy are active participants in the program, as are supportive specialties including pediatric radiology, immunology and medical genetics.

The Southwest Oncology Group Pediatric Divisions' central objective is the delineation of increasingly effective means for treating various types of childhood malignancies utilizing the combined efforts of the participating institutions in protocol design and implementation. These collaborative studies form the basis of the U.M.C. Department of Pediatrics' clinical research program in oncology. Studies are currently in progress for acute lymphocytic leukemia, acute granulocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, histiocytosis X, Wilms' tumor, neuroblastoma, rhabdomyosarcoma, osteogenic sarcoma, Ewing's sarcoma, brain tumor and malignant teratoma.

In addition to participating in the SWOG clinical research studies, the U.M.C. disciplines are active in committee functions and protocol development. The U.M.C. Department of Pediatrics is serving as the coordinating institution for the SWOG ALinC 13 pilot and final classification and treatment protocols. ALinC 13 will be the next SWOG pediatric front-line study for acute lymphocytic leukemia.

BIBLIOGRAPHIC REFERENCES: Pullen, J., Crist, W., Falletta, J., Humphrey, B., Metzgar, R., van Eys, J., Vogler, L.: Immunologic profiles in childhood acute lymphocytic leukemia (ALL). Proc AACR 21:247, 1980, Frankel, L.A., Wang, Y.M., Pullen, J., Nitschke, R., Doering, E.J.: High dose intravenous (IV) methotrexate (MTX) with an intrathecal (IT) boost in the maintenance of acute lymphocytic leukemia (ALL) in children. Proc ASCO 21:389, 1980.

**258. TREATMENT OF CHILDHOOD CANCER**

*Freeman, A. I.*, Rosweli Park Memorial Inst., Dept. of Pediatrics, *666 Elm St., Buffalo, New York*, 14263, United States of America

The current success in treating a number of types of childhood cancer is the result, in large part, of therapeutic research conducted by the cooperative pediatric cancer groups. Because most childhood cancers are rare, it is only through this mechanism that adequate numbers of patients can be accrued in reasonable lengths of time and that therapeutic questions can be answered. We will participate in the pediatric division of the Southwest Oncology Group (SWOG) so that our patient population can be used to answer treatment questions which would be impossible to answer were we to conduct only single institution studies.

There are some pediatric solid tumors for which the accrual, even in cooperative groups, is insufficient for meaningful therapeutic studies to be conducted. However, a number of intergroup studies are presently active and we plan to participate in these studies through the pediatric division of SWOG. Specifically, we will continue to enter patients on the National Wilms' Tumor Study, the Intergroup Ewing's Sarcoma Study, the Intergroup Rhabdomyosarcoma Study and the Intergroup Hodgkin's Disease Study. The diseases included in these intergroup studies are those which most commonly demand an interdisciplinary approach. We are strongly committed to this approach and have a good working relationship with the necessary cooperating specialities, including Radiation Therapy, Pediatric Surgery, Neurosurgery and Orthopedic Surgery.

As more children enter long-term remissions from their diseases, the identification, treatment and potential for prevention of complications of therapy have become significant areas for research. Our major areas of investigation include population based studies of major complications of radiation therapy and chemotherapy, investigations into the treatment and prevention of varicella-zoster infection in immunosuppressed patients and evaluation of the acute and long-term effects of radiation therapy and chemotherapy on various committed stem cell pools and the peripheral blood and bone marrows.

**259. SOUTHWEST ONCOLOGY GROUP**

*Dyment, P. G., Doering, E. J., Rothner, A. D., Cruse, R., Erenberg, G., Hahn, J. F., Kay, R., Steiger, E., Price, R., Gidwani, G., Marks, K., Deodhar, S. D.*, Cleveland Clinic Hospital, Section on Pediatric Hematology-Oncology, *9500 Euclid Ave., Cleveland, Ohio*, 44106, United States of America

This proposal involves a multi-disciplinary/multi-professional research approach to childhood malignancies. This proposal is supported by a clinical research and laboratory research team in a university affiliated pediatric medical center which is actively involved with the Pediatric Division of the Southwest Oncology Group (SWOG). Special emphasis is given to the combination of chemotherapy with other modalities of therapy such as radiation therapy and surgery. The Pediatric Oncology team consists of 2 pediatric hematologist-oncologists, 2 hematopathologists, a pediatric pathologist, a pediatric ophthalmologist, 3 child neurologists, a pediatric thoracic surgeon, an oncologic orthopedic surgeon, a pediatric gynecologist, 2 oncologic gynecologists, 2 social workers, a pediatric oncology nurse, 2 data technicians, a child psychiatrist and a tumor immunobiology support group of 5. All patients under 20 years of age who are admitted to the Cleveland Clinic Hospital are offered the opportunity to take part in SWOG protocols if one is open for their particular disease status. Members of the team are not only actively involved in patient care related to protocol research, but are heavily involved in both protocol design and committee work for SWOG.

BIBLIOGRAPHIC REFERENCES: Dyment, P.G., Doering, E.J., Asimont, L.A.: Probable cure of acute lymphocytic leukemia following relapses. JAMA 241:829, 1979. Sullivan, M.P., Perez, C., Silva-Sosa, M., Land, V., Chan, R., and Dyment, P.G.: Radiotherapy for testicular leukemia: Local control and subsequent clinical events. Cancer 46:508-515, 1980.

**260. SOUTHWEST ONCOLOGY GROUP (PEDIATRIC)**

*Fernbach, D. J., Starling, K. A., Steuber, C. P., Mukhopadhyay, N., Nix, W. L., Riccardi, V. M., Mahoney, D. H., Finegold, M., Hawkins, E. P., Gresik, V. M., Stenback, W. A., Spjut, H. J.*, Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas*, 77025, United States of America

1980 is the 23rd year that the Department of Pediatrics, Baylor College of Medicine, has participated in the activities of the Southwest Oncology Group (SWOG). The initial purpose of this group was to develop better methods of treatment for the control or cure of cancer in children. If a cure cannot be achieved, therapy is directed toward palliation of the disease, its consequences, prolonged survival, and perhaps most importantly, quality of survival. During the past few years multidisciplinary treatment programs have been developed and greater emphasis has been directed toward the etiology and pathophysiology of these diseases. This unit participates in all activities of the Pediatric Division. These activities include: Phase I studies of new chemical or biological agents; Phase II studies utilizing single or multiple agents in various disease categories; and Phase III studies, most of which are multidisciplinary, striving to determine the best combinations of therapy for control or cure of childhood cancer. Studies of the immunologic defects associated with various malignancies and immunotherapy directed toward eradication of various malignancies have been enlarged both within the Group and independently within this unit. Other areas of investigation relate to the epidemiology of malignant disease, the natural history of individual neoplastic disorders, and evaluations of methods to control the complications resulting from the disease or therapies. Particular emphasis has been given to determining prognostic factors and toward stratifying clinical case material accordingly in order to improve the basic study design. The biostatisticians have long been an integral part of the group's chemotherapy studies. Their role has been expanded to involve all multidisciplinary activities. Approximately 6 years ago the disciplines - radiotherapy, pathology, and surgery - began active participation in all group studies. With the separation of the Pediatric Division of SWOG from the Adult Division, all disciplines have been given equal status and participate in protocols from their inception.

BIBLIOGRAPHIC REFERENCES: D'Angio, G.J., Beckwith, J.B., Breslow, N.E., Bishop, H.C., Evans, A.E., Farewell, V., Fernbach, D.J., Goodwin, W.E., Jones, B., Leape, L.L., Palmer, N.F., Tefft, M., and Wolff, J.A.: Wilms' tumor: An update. Cancer 45:1791-1798, April, 1980. Sotelo-Avila, C., and Starling, K.A.: Wilms' tumor in a patient with an incomplete form of Beckwith-Wiedemann syndrome. Pediatrics 66:121-122, July, 1980.

**261. SOUTHWEST ONCOLOGY GROUP (PEDIATRICS)**

*Van Eys, J., Cangir, A., Sutow, W. W., Sullivan, M. P., Jaffe, N., Ried, H. L., Culbert, S. J., Frankel, L. S., Copeland, D. R., Hoots, W. K., Ramirez, I., Strong, L. C.*, University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Pediatrics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Investigative clinical therapeutic studies in children with acute leukemia, malignant lymphoma, histiocytosis X, and malignant solid tumors (brain tumors, neuroblastoma, Wilms' tumor, osteogenic sarcoma, Ewing's sarcoma, soft tissue sarcoma, and miscellaneous malignant neoplasms) are conducted in four areas: (a) Phase I coordinated studies of human pharmacologic and toxicologic aspects of new anticancer agents and new combinations and dosage regimens; (b) Phase II systematic investigations of the effectiveness of individual anticancer agents or treatment programs in specific tumors; (c) Phase III comparative evaluations of selected drugs and/or therapy regimens; and (d) specific laboratory investigations into immunology and clinical pharmacology. The functioning cooperative group study mechanism is utilized to increase the size of the study populations and to shorten the duration of the study.

Independent investigative probes are undertaken to explore leads resulting from or directed toward group studies. Several intergroup and national studies, ongoing and projected (National Wilms' Tumor Study, Intergroup Rhabdomyosarcoma Study, Intergroup Ewing's Sarcoma Study, Hepatoma Study, Hodgkin's Disease Study) are included.

This research will be executed in an integrated multimodal manner. Attention will be given to centralized data management

for the individual specialities of pediatrics, surgery, radiotherapy, pathology and laboratory support. Special attention will be given to clinical pharmacology and the immunological investigation required for optimal execution of current protocols employing high dose methotrexate or protocols requiring classification of lymphoid malignancies in order to establish proper therapy assignment.

BIBLIOGRAPHIC REFERENCES: Ramirez, I., Richie, E., Wang, Y-M, and van Eys, J.: The effect of L-ascorbic acid in vitro on lymphocyte reactivity to mitogens. Presented at the April 1979 FASEB meeting. Fed. Proc. 38:763, March 1979, 1979 (Abstract-2825). Ramirez, I., van Eys, J., Carr, D., Carter, P., Coody, D., and Taylor, G.: Malnutrition in children with malignancies. In: Proceedings of American Association for Cancer Research, and American Society of Clinical Oncology (Abstract) 21:378, May 1980.

**262. CHILDREN'S CANCER STUDY GROUP A**

*Shahidi, N. T.,* University of Wisconsin, Madison Campus, Medical School, Dept. of Pediatrics, *450 N. Randall Ave., Madison, Wisconsin,* 53706, United States of America

The members of the Children's Cancer Study Group, using mutually agreed upon protocols, conduct clinical investigations regarding optimal therapy of children with leukemia and solid tumors. The aim of such protocols is to evaluate therapeutic regimens, often combining surgery, radiotherapy, and chemotherapy, in an effort to increase disease-free survival and improve the cure rate of these illnesses. In addition, information regarding supportive care, use of blood products, toxicity, and survival is gathered and evaluated.

**263. CHILDREN'S CANCER STUDY GROUP A**

*Honig, G. R., Baum, E. S., Maurer, H. S., Gaynon, P., Morgan, E. R., Nicklas, J. W., Raffensperger, J. G.,* Northwestern University, Chicago Campus, Children's Memorial Hospital, *2300 Children's Plaza, Chicago, Illinois,* 60611, United States of America

The Children's Cancer Study Group A is composed of a group of cooperative pediatric centers, and provides an administrative and communicative structure for the performance of cooperatively designed clinical studies for the treatment of children with leukemia and solid tumors. These investigations involve a multidisciplinary approach including multiple agent chemotherapy, surgery, radiation, immunotherapy, and other modalities. The objective of these studies is to establish with maximum efficiency therapeutic regimens for these diseases that will provide an optimal outcome, with minimal untoward effects.

**264. CHILDREN'S CANCER STUDY GROUP A**

*Albo, V. C.,* Children's Hospital of Pittsburgh, *125 De Soto St., Pittsburgh, Pennsylvania,* 15213, United States of America

The Children's Cancer Study Group is a multi-disciplinary organization formed to cooperate in research into malignant diseases in children: specifically, to study the factors which may cause or influence these diseases, and to develop, evaluate and improve methods of treatment.

The primary objective of the cooperative group has been to evaluate new biological and chemotherapeutic agents in the treatment of acute leukemia and solid tumors in childhood, and find new and better ways of using the already known agents. This evaluation is done by pediatric oncologists, surgeons, radiotherapists, pathologists and immunologists within the cooperating institutions which make up the group.

It is also our objective to provide supportive care for these children with leukemia and solid tumors, which will enable all children who desire to do so to participate in our protocol studies. This supportive care includes financial supportive care (domiciliary care, travel assistance, outpatient costs, etc.), social service assistance, as well as medical supportive care.

**265. CHILDREN'S CANCER STUDY GROUP A**

*Lahey, M. E.,* Utah Higher Education System, University of Utah, School of Medicine, Dept. of Pediatrics, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

We propose to collaborate with other members of CCSG as well as with other members of other cooperative study groups, in research on leukemia, malignant solid tumors and closely related disorders in children. The chief purpose of the CCSG is to cooperate in several aspects of research in malignant disease in children (i.e., the natural history, epidemiology) and in particular to develop, evaluate and improve methods of diagnosis, prognosis and treatment of malignant disease in children.

Special emphasis will be placed on the study of new combinations and new schedules of already established chemotherapeutic agents as well as on the evaluation of new anti-cancer agents and new modalities of therapy.

The Principal Investigator is Chairman of the Histiocytosis Committee and has recently received approval by CIB of a new protocol designed to study this disorder in depth with particular attention to clinical and histologic features of prognostic significance, improved therapy and comprehensive immunologic evaluation. The prognostic significance of certain clinical features developed by CCSG has been tested and acclaimed by other chemotherapy groups.

**266. CHILDREN'S CANCER STUDY GROUP A**

*Gross, S.,* Case Western Reserve University, School of Medicine, Dept. of Pediatrics, *2109 Adelbert Rd., Cleveland, Ohio,* 44106, United States of America

CCG has the expertise to combine whole group protocol studies with small intra-group investigations of tumor biology. Large scale clinical programs are needed to consolidate data accrual of the past decade. Included in small group studies are those utilizing data on experiments in nature, i.e., adenosine deaminase (ADA) deficiency; anti-cancer effects of interferon; anti-tumor antibodies (common ALL, neuroblastoma); transplantation (allogeneic, autologous) biology; autologous lymphocyte therapy; radiosensitizer therapy; limb salvaging techniques/aggressive metastatic surgical attack; and diagnostic imaging procedures. Induced ADA deficiency can be applied to the study of T-cell leukemia and to the nature of lymphoblast modulation. Interferon data can be applied to the study of non-T ALL, non-Hodgkin's lymphoma and osteosarcoma and to the nature of tumor cell death. Anti-(common) ALL antibody studies can be applied to the development of common ALL and non-T, non-B lymphoma protocols. Specific anti-neuroblastoma antibody data can be applied to the development of randomized studies comparing chemotherapy and chemotherapy plus adjuvant antibody therapy. Allogenic transplantation for AML can be expanded to relapsing high risk ALL and high risk lymphoma. Autologous marrow transplantation rescue is applicable for megadose therapy studies of leukemia, lymphoma and a variety of solid tumors and as a means of evaluating techniques for identifying occult tumor burdens. Similarly, autologous lymphocyte infusion into brain tumors can test the hypothesis that such malignancies occupy immunologically priviledged sites and in turn be incorporated into a randomized radiosensitizer therapy study. Conflicting osteosarcoma data can be resolved by comparing pre-op megadose therapy to surgery alone (including evaluation of transfer factor, limb salvaging, and evaluation of the time/therapy sequence in treatment of metastatic disease). Extensive investigation of new agents is required in high risk Wilms' and Ewing's sarcoma and rhabdomyosarcoma. Efficacy studies of appropriate imaging techniques are mandated in virtually all protocols in which tumor delineation is essential. And in all studies active participation by nurse specialists should be encouraged in order to enhance protocol development.

**267. CHILDREN'S CANCER STUDY GROUP**

*Leikin, S. L., Reaman, G., Movassaghi, N., Randolph, J. G.,* Children's Hospital National Medical Center, *111 Michigan Ave. N.W., Washington, District of Columbia,* 20010, United States of America

Our research objective is to pursue our investigations of leukemia and malignant tumor therapy by participation in Children's Cancer Study Group (CCSG). This organization is composed of pediatric hematologists/oncologists, radiotherapists, surgeons, and pathologists from a number of pediatric and cancer institutions, and is involved in protocol studies of pediatric malignancy as formulated by the members of the group. The investigations include the chemotherapy, radiotherapy and immunotherapy trials in acute childhood leukemia and drug therapy trials in solid tumors of the young in conjunction with surgery and radiotherapy. Data on the natural history, complications of treatment and the survival of these patients are collected on an ongoing basis. Statistical supervision is maintained

in all of the protocol studies, and in most cases these studies are randomized to prevent bias.

**268. CHILDREN'S CANCER STUDY GROUP**

*Klemperer, M. R., Segel, G. B., Ettinger, L. J., Putnam, T. C., Emmens, R., Rabinowitz, R., Wood, B., Sahler, O. J., Rubin, P., Anderson, V.,* University of Rochester, School of Medicine & Dentistry, Dept. of Pediatrics, *601 Elmwood Ave., Rochester, New York,* 14627, United States of America

This proposal requests continued support for an established children's cancer program at the University of Rochester Medical Center. The objectives of this program are: (1) Optimal patient care and continual improvement in such care through the utilization of collaborative multidisciplinary protocols of a cooperative cancer study group; (2) the evaluation of new approaches to cancer therapy in such areas as new agent development, immunotherapy and supportive care; (3) the definition of factors which may cause and do effect the course of neoplastic disease; (4) the education of practicing physicians, subspecialists, house officers, medical students, nurses and social workers in the diagnosis, treatment and management of children with cancer; and (5) the participation of the Pediatric Hematology-Oncology Unit in all appropriate programs of the University of Rochester Cancer Center.

BIBLIOGRAPHIC REFERENCES: Nusbacher, J., Rosenfeld, S.I., Leddy, J.P., Klemperer, M.R., and MacPherson, J.L.: The leukokinetic changes and complement activation association with filtration leukophoresis. Experimental Hematology 7(Suppl. 4):24, 1979. Segel, G.B., Kovach, G., and Lichtman, M.A.: Human lymphocyte plasma membrane sodium-potassium activated adenosine triphosphatase: Kinetic characteristics, substrate specificity and effect of phytohemagglutinin. J. Cell. Physiol. 100:109-117, 1979.

**269. CHILDREN'S CANCER STUDY GROUP**

*Nesbit, M. E.,* University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The objective of this grant is to facilitate the continued involvement of the University of Minnesota pediatric oncology group in the multi-institutional cooperative therapeutic and non-therapeutic studies conducted by the Children's Cancer Study Group. These studies are conducted using the 'team approach' which involves individuals from a wide range of disciplines. Specific areas of investigation include: design of new therapeutic approaches, assessment of the usefulness of bone marrow transplantation of resistant leukemias, testing of new agents, the treatment and biology of neuroblastoma, drug pharmacology, and the occurrence of iatrogenic effects of treatment in long-term survivors. It is anticipated that the pediatric oncology group at the University of Minnesota will continue to provide significant input into the direction, planning, development and conduct of the clinical investigations and ancillary studies conducted by Children's Cancer Study Group.

BIBLIOGRAPHIC REFERENCES: Shapiro, R., Kim, Y., Michael, A.F., Gerrard, J.M., Nesbit, M., Coccia, P.F., Ramsay, N.K.C., Krivit, W.: L-asparaginase Induced Hypocomplementemia in Acute Lymphocytic Leukemia (ALL) of Childhood. The American Journal of Pediatric Hematology-Oncology. 1:5-7, 1979

**270. CHILDREN'S CANCER STUDY GROUP - UNIVERSITY OF OREGON**

*Neerhout, R. C., Wolff, L. J., Campbell, J. R., Houghton, D. C., Stevens, K. R., Harrison, M. W., Smiley, S.,* Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Pediatrics, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon,* 97201, United States of America

This program is to help support the participation of the Pediatric Oncology group at the University of Oregon Health Sciences Center in the Children's Cancer Study Group. The Pediatric Oncology program is a multidiscipline group formed to improve the quality of care of children with cancer in Oregon and adjacent states. The program includes four major commitments: 1) Patient care, 2) research, 3) teaching, and 4) continuing education of the public and health care professionals. Although this program deals primarily with patient care and research as it relates to patient care, all aspects of the program are interrelated and thus described in the text. The basic aim of the proposal is to provide for clinical research utilizing the patient population in this geographic area by participating in Children's Cancer Study Group treatment and protocols. Emphasis is placed on combining the best of multidisciplinary cancer therapy with strong psychosocial support for the patient and the family.

**271. CHILDREN'S CANCER STUDY GROUP**

*Feig, S. A.,* University of California, Los Angeles Campus, School of Medicine, Dept. of Pediatrics, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

The multidisciplinary pediatric oncology program at UCLA will participate in the clinical research programs of the Children's Cancer Study Group (CCSG). This will allow UCLA physicians and patients to take part in clinical oncology studies which could not be undertaken in a single institution. UCLA has a program which focuses on certain pediatric neoplasms which have not benefitted from the recent advances in the oncologic armamentarium: a)recurrent acute lymphoblastic leukemia, b) acute myeloblastic leukemia, c) neuroblastoma, and d) histiocytosis-X. UCLA will participate in the development of new investigative programs dealing with the biology, diagnosis, and treatment of these neoplasms with CCSG. These programs will make use of the extensive experience of the UCLA team in the areas of bone marrow transplantation and tumor immunology. In addition, UCLA will initiate local pilot studies relevant to basic and applied pediatric oncology. The data generated by these studies will aid in the development of future limited-institution and Group-wide clinical studies.

**272. CHILDREN'S CANCER STUDY GROUP**

*Tubergen, D. G., Favara, B., Chang, J., Daniel, W., Odom, L., Heideman, R.,* Children's Hospital, Dept. of Oncology & Hematology, *1056 E. 19th Ave., Denver, Colorado,* 80218, United States of America

Children's Cancer Study Group is engaged in conducting clinical research programs which have been developed to improve the care and survival of children with malignant disease. This is accomplished by means of treatment protocols conducted on a limited institution (pilot) basis, groupwide studies, and intergroup studies (such as Wilms' tumor, Hodgkin's disease and rhabdomyosarcoma studies).

The Oncology Center personnel at The Children's Hospital will participate in the design and execution of all such protocols. We will provide to the Group a well-established multidisciplinary team with a well-organized data collecting system. Our research capability will permit us to participate in cell surface marker studies on a local basis only or as a limited reference source. Local protocols conducted over the past three years may provide useful information for new protocol design within the group.

**273. CHILDREN'S CANCER STUDY GROUP (CCSG)**

*Ablin, A. R., Wara, W., Matthay, K., Zoger, S., Kushner, J. H., Mentzer, W., deLorimier, A., Harrison, M., Rosenau, W.,* University of California, San Francisco Campus, School of Medicine, Dept. of Pediatrics, *551 Parnassus Ave., San Francisco, California,* 94122, United States of America

OBJECTIVES: 1. Our major objective during this grant period is to meaningfully contribute to the design, execution and evaluation of protocols of the Children's Cancer Study Group. Group studies, which are chaired by members of our oncology team, are, of course, of special interest to us and we plan to devote our major energies to these areas, i.e., germ cell tumors, hepatomas, interferon cell surface characteristics in ANLL, pneumococcal vaccine, half-body sequential radiation for relapsing histiocytosis, medulloblastoma, misonidazole with radiation therapy. 2. During this grant period, we plan to develop new strength in laboratory oncology, extending our interests beyond the clinic and into areas which are compatible with the Group's interests, specifically in the areas of cell surface characteristics of ANLL and closer examination of white cell function in the pediatric patient with malignancy and infection. 3. To participate in the evaluation of phase II agents in the treatment of childhood malignancies. 4. To make significant contributions to the Group effort in the pursuit of its goals in both the scientific and the administrative areas. 5. To further develop and improve

the multidisciplinary approach to problem solving in childhood clinical cancer research both in our institution and in those in our referral area.

**274. COOPERATIVE STUDY OF CHILDREN'S CANCER**

*Baehner, R. L., Weetman, R. M., Provisor, A. J., Wagner, V. M., Boxer, L. A., Chilcote, R. R., Grosfeld, J. L., Mirkin, D. L., Spelser, B. L.*, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Pediatrics, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

This proposal describes the multimodal program to be employed by the Indiana University Pediatric Oncology Staff as an active participant in the Children's Cancer Study Group (CCSG). The program will be implemented by a) registering and enrolling all available patients into CCSG protocol studies; b) carefully attending to the quality control of every aspect of the protocol; c) maintaining communication between the members of the multimodal team to ensure that all are kept informed about the management of each study patient as well as the results of current CCSG protocols; d) fostering an environment of scientific excellence; e) contributing ideas to and serving on study committees for CCSG. This program should result in the optimum treatment for children with cancer and at the same time provide a data base for the development of better treatment modalities for the future.

BIBLIOGRAPHIC REFERENCES: Weetman, R.M., Baehner, R.L.: Childhood acute leukemia. In Current Therapy. F.C. Bartter et al. (eds.) pp. 294-300, 1979. Wagner, V.M., Baehner, R.L.: Correlation of the FAB Morphologic Criteria and Prognosis in Acute Lymphocytic Leukemia of Childhood. Amer. J. Pediatric Hem/Onc. Vol. 1(2) 1979.

**275. CHILDREN'S CANCER STUDY GROUP**

*Evans, A. E., Norris, D., Raney, R. B., Koch, P., Toledano, S., Rohrbaugh, T., Chatten, J., Bruce, D., Templeton, J.*, Children's Hospital of Philadelphia, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

The Children's Hospital of Philadelphia (CHP) is a primary treatment center for children with malignant diseases. It also has been designated a Pediatric Cancer Research Center (USPHS Grant No. 14489). As a member institution of the Children's Cancer Study Group (CCSG) it will pursue the study and treatment of pediatric oncologic disorders via the Phase II and III protocols of CCSG. Chemotherapy and immunotherapy will be utilized alone or in conjunction with surgery and/or radiation therapy, as indicated by the study protocols, in efforts to devise more effective and less toxic methods of improving survival in children with leukemia and solid tumors. The Children's Hospital of Philadelphia is one of the four CCSG institutions performing bone marrow transplantation as a mode of therapy for patients with acute non-lymphocytic leukemia (ANLL). Co-investigators from Surgery, Pathology, Diagnostic Radiology, Radiation Therapy, Dentistry and Infectious Diseases will participate in the development and conduct of these studies. Through the use of the Intergroup Study mechanism, collaboration with other Cooperative Cancer Study Groups will achieve statistically valid study of the less frequently occurring malignancies. The CHP will also actively participate in the Group's efforts directed at assessing the late effects of cancer therapy.

**276. CHILDREN'S CANCER STUDY GROUP**

*Lukens, J. N., Heller, R. M., Stroup, S. L., O'Neill, J. A., Griffin, P. P., Kasselberg, A. G., Collins, R. D., Roloff, J. S.*, Vanderbilt University, School of Medicine, Dept. of Pediatrics, *21st Ave. S. & Garland, Nashville, Tennessee*, 37232, United States of America

The overriding purpose of this proposal is the improvement of childhood cancer treatment and rehabilitation - both locally and nationally - through institutional participation in Children's Cancer Study Group (CCSG) activities. Inherent in this objective are the following corollary goals, which may be viewed as the means by which the primary purpose is to be achieved: 1. Enlist the participation of patients referred to Vanderbilt and its affiliate, the Oschner Clinic, in CCSG research protocols so as to facilitate the expeditious conduct and timely conclusion of Group-wide clinical studies. 2. By drawing on Vanderbilt's professional resources, to further augument the Group's capabilities for scientific inquiry relative to pediatric oncology, protocol development, and data analysis. 3. Through controlled clinical trials, to assess new modalities of therapy, new combinations and new schedules of therapy, and newly developed pharmacologic agents (Phase II drugs). 4. Participate in Group-wide non-therapeutic investigations which are designed to probe the biology of pediatric tumors; define the relative sensitivity of various diagnostic procedures and imaging techniques; and further characterize the demographic features of selected tumors. 5. Provide students and professionals in training with the background necessary to appreciate and evaluate research regarding the biology and treatment of childhood cancer.

**277. CHILDREN'S CANCER STUDY GROUP**

*Miller, D. R., Steinherz, P. G., Allen, J. C., Tan, C.*, Memorial Hospital for Cancer & Allied Diseases, Dept. of Pediatrics, *1275 York Ave., New York, New York*, 10021, United States of America

The Children's Cancer Study Group is a multidisciplinary cooperative group of investigators from 26 institutions in the United States and Canada collaborating on the development, implementation and completion of prospective, randomized clinical trials in pediatric hematologic malignancies and solid tumors, including acute lymphoblastic leukemia (ALL), acute nonlymphoblastic leukemia (ANLL), brain tumors, lymphomas (non-Hodgkin's and Hodgkin's), Wilms' tumor, neuroblastoma, rhabdomyosarcoma, bone tumors, hepatoblastoma, 'histiocytosis X', and retinoblastoma. Natural history, biologic characterization of cancer (pathology, immunology, biochemistry), prognostic factors, late effects and supportive care aspects are also stressed in these studies involving pediatric oncohematologists, surgeons, pathologists, diagnostic and therapeutic radiologists, neurologists, psychiatrists, psychologists, cell biologists, immunologists, and infectious disease specialists. New agent Phase II trials for patients failing initial therapy and new modalities of therapy, including bone marrow transplantation, are additional major thrusts of the cooperative group. MSKCC - NYH-CMC (and its affiliates) has been a major contributor to the efforts of the Group. This research proposal outlines the center's participation in present and future CCSG endeavors at the executive level as well as in the development of new pilot studies for eventual groupwide participation.

BIBLIOGRAPHIC REFERENCES: Bestak, M., Miller, D.R., and Mouradian, J. : Neurofibromatosis, juvenile chronic granulocytic leukemia and dermal histiocytosis. Amer. J. Dis. Child, 133:831-833, 1979. Luban, N.L.C., Mouradian, J., and Miller, D.R.: Intestinal perforation during remission of ALL. J. Pediatr. 94:409-410, 1979.

**278. THE CHILDRENS CANCER STUDY GROUP**

*Finklestein, J. Z.*, University of California, Los Angeles Campus, Los Angeles County Harbor General Hospital, *1000 W. Carson St., Torrance, California*, 90509, United States of America

OBJECTIVE: The purpose of this project is to continue and expand the active participation of Harbor General Hospital and affiliated institutions in all phases of the Children's Cancer Study Group.

The research involves a multi-disciplinarian approach to the clinical investigation of childhood cancer with special emphasis on chemotherapy of acute leukemia and solid tumors of childhood with collaborative protocols developed by the Children's Cancer Study Group. We will continue to participate in the study and the treatment of pediatric oncologic disorders by means of Phase I, II, and III Protocols. In addition, pertinent questions regarding natural history, treatment and epidemiology of childhood cancer will be investigated.

APPROACH: The results of therapies are recorded by the institutions' pediatric oncology staff, including Data Managers, and Protocol Nurse Coordinators, supervised by Subspecialists in Pediatric Oncology. Information is forwarded to the Operations Office for detailed statistical analysis.

The ultimate benefit is that the investigation involves controlled clinical trials in leukemia and solid tumors of childhood, controlled evaluations of newly developed therapeutic agents and controlled studies of the effects of immunotherapy and immunosuppression. Children participating in this project will benefit by being offered the most up-to-date methods of diagnosis, treatment and management of their disorders. The program

seeks a scientific approach to a comprehensive, therapeutic investigation of childhood cancer.

**279. CHILDREN'S CANCER STUDY GROUP**

*Gilchrist, G. S., Bruckman, J. E., Burgert, E. O., Evans, R. G., Goellner, J. R., Kelalis, P. P.,* Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota,* 55901, United States of America

The primary objective of the proposal is to support Mayo Clinic's participation in the Children's Cancer Study Group. This will allow continuing support for the cooperative group activites of the Pediatric Oncology Group at Mayo Clinic and its satellites in Des Moines, Iowa; Fargo, North Dakota; and Duluth, Minnesota.

The ultimate goal of the proposal is to develop methods for long-term control and cure in a wide variety of malignant diseases in children while evaluating and minimizing the adverse short-term and long-term effects of treatment.

Clinical research in pediatric cancer demands a coordinated team effort involving surgeons, therapeutic radiologists, pathologists, pediatric oncologists, immunologists, histochemists, pharamcologists and radiologists. Solid tumor treatment protocols are becoming increasingly more complex and accurate pretreatment staging and standardized operative, radiotherapuetic and chemotherapeutic procedures are essential. Since pediatric surgeons, pediatric urologists, orthopedic oncologic surgeons and diagnostic radiologists play a major role in diagnosis, staging and surgical therapy of solid tumor patients and also participate actively in postoperative evaluation, reporting and data analysis, their formal involvement in this program is critical for maintaining the highest level of clinical and laboratory research within the Children's Cancer Study Group. In addition, psychosocial evaluation and support for the patient and family is considered essential to the successful outcome of this type of clinical research and can also provide a basis for the development of clinical research studies for evaluating the psychosocial impact of cancer on children and their families.

**280. CHILDREN'S CANCER STUDY GROUP**

*Higgins, G. R.,* Children's Hospital of Los Angeles, *4650 Sunset Blvd., Los Angeles, California,* 90054, United States of America

The project proposes continuation of a comprehensive pediatric oncology program at Children's Hospital of Los Angeles (CHLA). This program is designed to improve the treatment of children with cancer by conducting clinical investigations as a member of Children's Cancer Study Group (CCSG) and by independently conducting other research which is directly related to the mission of CCSG. CHLA is a major pediatric referral center for the Pacific Southwest and has one of the largest pediatric oncology services in the nation. An interdepartmental program has developed at CHLA which involves basic and clinical scientists and has evolved into a multidisciplinary model for the management of pediatric cancers.

The participation of the investigators of CHLA in CCSG enables quantitative comparative clinical investigations aimed at establishing the best mode of any cancer therapy. The unique resources of CHLA permit the development of new therapeutic approaches for groupwide application. These include participation in the National Cancer Institute Phase I Working Group and the Late Effects Study Group, the evaluation of new dose schedules and combinations of established agents predicted by in vitro and in vivo pharmacological studies, immunological characterization of selected neoplasms, effects of cancer and its treatment on hematopoiesis, intensive chemotherapy in the protected environment, optimum nutritional support in childhood malignancies, approaches to psychosocial rehabilitation of the pediatric cancer patient and family, and pre-clinical studies in molecular and cellular pharmacology, tumor cell biology, carcinogenesis, in vitro and in vivo tumor model systems. A network of community physicians participates in the CCSG Cancer Control Program for Clinical Cooperative Groups under the sponsorship of CHLA which enables the use of optimal therapy in children who are not referred for initial cancer care.

Through the proposed continuation the comprehensive program at CHLA will seek as its ultimate goal an integrated therapeutic and investigative approach to childhood cancer.

**281. CHILDREN'S CANCER STUDY GROUP - CHAIRMAN'S GRANT**

*Hammond, G. D.,* University of Southern California, School of Medicine, Dept. of Pediatrics, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

Children's Cancer Study Group is an organization of Pediatricians, Surgeons, Radiation Therapists, Pathologists, Immunologists, Statisticians and their support staff at 29 major institutions in the United States and Canada having special research and education programs in pediatric oncology. This Group collaborates on the concept, design, conduct, analysis and reporting of clinical investigations of cancer in children.

Standing Committees have been established to faciiitate the investigative activities of the Group and to stimulate the development of multidisciplinary investigative teams within each institution. These Standing Committees include the Surgical Committee, Radiation Therapy Committee, Pathology Committee, Special Studies-Supportive Care Committee, Tumor Imaging and Diagnostic Radiology Committee, Oncology Nursing Committee, Immunology Committee, and the Late Effects of Cancer in Children Committee. These Committees are integral and essential segments of the Group's investigative activities, providing multimodality therapeutic research.

Study Committees are appointed to develop investigative protocols for the conduct of clinical trials research in the areas of Acute Leukemia, Solid Tumors, Phase I and II Single Agents and Special Studies that are not inherently cancer therapeutic. The Study Committees receive advice and guidance from the Executive Committee, Standing Committees and the Statisticians.

The direction and coordination of these activities require an Operations Office providing staff and facilities for executive direction, Group communications and data collection, verification, monitoring, processing, analysis and reporting. These functions require the overall direction of the Group Chairman, supervision by the Administrative Director and the Group Statisticians and a close working relationship between these persons and the Operations Office Staff.

This grant application requests support for the Operations Office, including the activities of the Group Chairman, Administrative Director, Statisticians and the Data Management, Administrative and Clerical Staff, and for the Standing Committees to provide overall direction of the Group in multidisciplinary investigations that lead to improvements in the survival and cure rate of children with cancer.

BIBLIOGRAPHIC REFERENCES: Gaynon, P., Baum, E., Greenberg, L., Krivit, W., Hammond, D., Taylor, S: A Phase III Trial of Cis-Platinum Diammine Dichloride (DDP) (NSC 119825) in Refractory Childhood Tumors: A CCSG Trial. Proc Amer. Assn. Cancer Res. 1979 (abstr). Krivit, W., Chilcote, R., Pyesmany, A., Anderson, J., Hammond, D.: An Initial Report of a Phase III Trial Comparing Vindesine and Vincristine for Acute Lymphocytic Leukemia of Childhood Cancer Chemo. And Pharmacology 1:1-4 1979.

**282. CHILDREN'S CANCER STUDY GROUP**

*Kisker, C. T., Strayer, F. H., Davidson, J., Tannous, R., Brandes, M. M., Linder, M. L., Dick, F., Fox, M., Tewfik, H., Bischof, C.,* University of Iowa, School of Medicine, Dept. of Pediatrics, *Jessup Hall, Iowa City, Iowa,* 52240, United States of America

The aims of this project are to participate in the Children's Cancer Study Group by 1) placing childhood cancer patients on CCSG protocols, 2) working on CCSG committees to evaluate, formulate and write research protocols, 3) providing a comprehensive educational program for members of the medical community and allied health personnel concerning pediatric oncology and its treatment, 4) providing comprehensive educational services to patients and the public concerning pediatric oncology, its treatment and the value of cooperative studies, 5) sharing with Children's Cancer Study Groups results of pediatric cancer research currently being conducted at the University of Iowa, and 6) conducting investigations into computer-assisted management of patients on CCSG protocols and into computer-assisted collection and transmission of research data on CCSG study patients. Iowa is among the upper quartile of CCSG institutions in the number of patient entries per month and in providing data for CCSG studies. This project will allow Iowa to continue to

expand its participation in these studies through patient entry and data retrieval. The principal investigator is involved in the development of two CCSG studies and the review of two studies. The project will allow both the principal investigator and others to increase their participation in development and review of CCSG studies. Continued participation in CCSG studies will allow dissemination of information concerning childhood cancer to a large number of medical, paramedical and lay persons in the Midwest through the educational activities of the Iowa Center personnel. Research investigations currently being done at Iowa will be utilized in the protocol committees in which Iowa investigators participate. Finally, the development of computer-assisted patient and data management at other centers participating in CCSG studies is planned.

**283. CHILDREN'S CANCER STUDY GROUP**

*Heyn, R. M., Ertel, I., Hutchinson, R. J., Hanash, S., Holland, R., Heidelberger, K., Schnitzer, B., Waskerwitz, M., Hanson, T.,* University of Michigan, Ann Arbor Campus, Medical School, Dept. of Pediatrics & Communicable Diseases, *1335 E. Catherine St., Ann Arbor, Michigan,* 48104, United States of America

The Children's Cancer Study Group is engaged in carrying out clinical research studies which have been developed by senior investigators in the group and approved by the NCI. These programs, which are designed to improve the care and survival of children with leukemia and solid tumors, include both Phase II and Phase III studies. Phase II studies are primarily those involving new agents which have completed Phase I trial.

The current study for children with newly diagnosed acute lymphocytic leukemia involves stratification at diagnosis based on white blood count, age, and cell morphology. Remission is induced with prednisone, vincristine and L-asparaginase in all children and similar CNS prophylaxis is given to all except the good-risk group which is randomized to either intrathecal methotrexate or cranial irradiation and intrathecal methotrexate. All patients are then randomized for various maintenance programs to answer the question of whether it is advantageous to 1) give further intermittent intrathecal methotrexate and 2) various intermittent additive drugs to systemic chemotherapy with daily 6-mercaptopurine and weekly methotrexate orally.

Children with acute non-lymphocytic leukemia are induced with continuous infusion cytosine arabinoside for 7 days plus 3 daily doses of adriamycin, given at 2 week intervals. If remission is obtained, children with HLA sibling matches will receive bone marrow transplant. Those without such matches will enter a chemotherapy maintenance program involving cyclic versus continuous use of multiple agents.

Solid tumor studies include the intergroup studies for Wilms' tumor, Ewing's sarcoma and rhabdomyosarcoma. Studies for Stage I and II Hodgkin's disease and non-Hodgkin's lymphoma are being done in conjunction with other cooperative groups. Other Children's Cancer Study Group studies are current for brain tumors, osteogenic sarcoma, histiocytosis X, retinoblastoma, liver tumors and ovarian tumors.

BIBLIOGRAPHIC REFERENCES: Heidelberger, K.P., Schnitzer, B., Tilford, D., Poznanski, A.K., and Heyn, R. Marked skeletal involvement in sinus histiocytosis with massive lymphadenopathy. Accepted for publication in Skeletal Radiology, May, 1979. Lahey, M.E., Heyn, R.M., Newton, W.A. Jr., Shore, N., Smith, W.B., Leikin, S., and Hammond, D. Histiocytosis X: Clinical trial of Chlorambucil. A report from Children's Cancer Study Group. Accepted for publication in Medical and Pediatric Oncology, 1979.

**284. CHILDREN'S CANCER STUDY GROUP**

*Piomelli, S., Sitarz, A. L., Wolff, J. A., Weiner, M., Vora, S., Santulli, T. V., Chang, C. H., Blanc, W. A., Berdron, W. E.,* Columbia University, College of Physicians & Surgeons, Dept. of Pediatrics, *630 W. 168th St., New York, New York,* 10032, United States of America

The Division of Pediatric Hematology of Babies' Hospital (the Pediatric Section of the College of Physicians and Surgeons of Columbia University) has participated in the research activities of Children's Cancer Study Group since 1957. Patients have been and will continue to be entered in the clinical trials of this Group, directed at devising optimal therapy for children's cancer and evaluating biological and natural history factors which are important; a multidisciplinary approach to cancer therapy will be followed, both at the institutional and at a national group level. Children with cancer cared for by members of the Division will be entered in the studies of the Group: they will receive medical care standardized to Group requirements, including all required laboratory and diagnostic investigations; accurate records will be kept and transmitted promptly to Group Headquarters for evaluation. Members of the Division will actively participate in the development of the research strategy of new studies. They will participate in the development of the Group scientific program, development and conduct of protocols for Ewing's sarcoma, retinoblastoma and non-Hodgkin's lymphoma, improved modalities for supportive care and definition of biological aspects of childhood cancer, refinement of Pediatric Surgical Oncology techniques and cost effective imaging techniques and coordination of the Group Pathology activities.

The Division of Pediatric Hematology/Oncology will coordinate the clinical care of childhood cancer in the Columbia Medical Community. Related research activities within the Division will be developed and eventually expanded to Group trials. These presently include studies of biochemical markers of malignancy; means to decrease toxicity of chemotherapy; the relationship between nutrition, cancer and chemotherapy; newly developed varicella vaccine and epidemiological aspects of perinatal cancer. The interaction between the clinical activities of the Division of Pediatric Hematology/Oncology and the comprehensive Cancer Center of Columbia University will be further developed.

**285. CHILDRENS CANCER STUDY GROUP**

*Lampkin, B. C., Wong, K. Y., Harris, R., Neely, J., Lobel, J., Gruppo, R., Fischer, T., Meyer, R.,* Children's Hospital Medical Center, Dept. of Pediatrics, *3245 Burnet Ave., Cincinnati, Ohio,* 45229, United States of America

The overall objective of this proposal is to improve the diagnosis, treatment and rehabilitation of children with cancer through participation in protocols designed by Children's Cancer Study Group, a mission similar to the objective of Children's Cancer Study Group.

The Children's Hospital Medical Center is the major pediatric center within a 50-75 mile radius of Cincinnati and is the only pediatric unit within Cincinnati. The University of Kentucky Medical Center, which is 85 miles from Cincinnati, collaborates with Children's Hospital Medical Center in a multidisciplinary approach to the diagnosis, treatment and investigation of children with cancer. The members of the team at both institutions include: hematology oncologists, surgeons, radiologists, radiotherapists, pathologists, nuclear medicine physicians and biochemists.

The research plan for participation in Children's Cancer Study Group by both Children's Hospital Medical Center and the University of Kentucky Medical Center consists of: (a) Participation by entering patients on protocols, (b) participation in committees to write protocols, (c) education of medical and paramedical personnel regarding cooperative studies in children with cancer; and (d) independent research in the fields of cell kinetics, biochemistry and immunology.

Participation by Children's Hospital Medical Center and the University of Kentucky Medical Center in Children's Cancer Study Group should improve the diagnosis, treatment and rehabilitation of children with cancer in the referral areas of the two institutions. The results of ongoing research programs at both institutions may serve as a background for groupwide application.

BIBLIOGRAPHIC REFERENCES: Blattner, W.A., McGuire, D.B., Mulvihill, J.J., Fraumeni, J.F., Lampkin, B.C., and Hananian, J.: Geneology of cancer in a family. JAMA 19:259-61, 1979.

**286. CHILDREN'S CANCER STUDY GROUP**

*Newton, W. A., Miser, A., Miser, J., Distelhorst, C., Mulne, L., Rothermel, K., Boles, E. T., King, D., Clatworthy, H. W.,* Children's Hospital, Dept. of Pathology/Pediatrics, *561 S. 17th St., Livingston Pike, Columbus, Ohio,* 43205, United States of America

This is a continuation of a cooperative inter-institutional study of cancer in children, utilizing multi-disciplinary approach to treatment of those types of cancer which are suited for scientific analysis in a reasonable period of time. The studies are designed to provide answers to questions concerning optimum management, and at the same time provide the individual institutions with the added strengths to supply their communities with a referral center for childhood cancer.

At the time of writing, there are 11 active protocols dealing with leukemia and 27 dealing with solid tumors, including Phase II studies. The principal protocol for ALL/AML is designed to determine the relative importance of front-end factors in prognosis, with randomized increased therapy during maintenance for those with known poor prognostic findings. The present AML protocol is an effort to improve survival and duration of remission in childhood AML by combining the two best therapies from CCSG 241 and CCSG 102.

Specific protocols currently being used are those for neuroblastoma, Stage III and IV; histiocytosis; retinoblastoma, unilateral and extraocular; brain tumors; osteogenic sarcoma; non-Hodgkin's lymphoma and ovarian tumors. On an intergroup basis, there are active protocols for rhabdomyosarcoma, Ewing's tumor both non-metastatic and metastatic, Hodgkin's disease and Wilms' tumor. Protocols being formulated and finalized are for bilateral retinoblastoma, brain tumors, nasopharyngeal carcinoma, and hepatoma.

In addition, ongoing Phase II protocols utilize a succession or combination of new therapeutic agents such as Vindesine, galactitol, Azapicyl, Prednimustine, beta-TGdR, cis-platinum, Poly I:Poly C and hexamethylmelamine.

BIBLIOGRAPHIC REFERENCES: Raney, R.B., Gehan, E.A., Maurer, H.W., Newton, W.A., Ragab, A.H., Ruymann, F.B., Sutow, W.W., and Tefft, M.: Evaluation of intensified chemotherapy in children with advanced rhabdomyosarcoma (Clinical Groups III and IV). Cancer Clinical Trials, 19-28, Spring, 1979.

### 287. CHILDREN'S CANCER STUDY GROUP

*Chard, R. L., Johnson, F. L., Pendergrass, T. W.,* Children's Orthopedic Hospital & Medical Center, Division of Hematology/Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

This proposal is for continuation of research into the natural history, treatment and epidemiology of the statistical conduct, design, collation, and publication of childhood cancer. It will continue to emphasize multimodal aspects of the Children's Cancer Study Group which has realized such excellent results in the past in Wilms' tumors and rhabdomyosarcoma and has now helped in defining acute childhood lymphocytic leukemia as more than one disease entity which requires different treatments for different groups. Also, treatment has been improved in osteogenic sarcoma and Ewing's sarcoma and, though advances are more meager, there have also been statistical improvements in survival of neuroblastoma patients. Childhood nonlymphocytic leukemia patients have also shown improved survival and the Children's Cancer Study Group has now combined in a Groupwide study to compare bone marrow transplantation in first remission to more standard conventional chemotherapy in a controlled fashion.

During the period from November, 1976 to December, 1979, 389 children with childhood cancer were seen at this institution; 182 with leukemia, 148 who were treated on study, 44 who were not on study, and 207 children with solid tumors. We have been a member of the Children's Cancer Study Group since 1959 and strong permanent referral patterns have been established. It is therefore anticipated that the patient load will continue to be stabilized and slightly increased over the next several years. A close working relationship with the adult leukemia center under Dr. E. Donnall Thomas at the Fred Hutchinson Cancer Research Center continues. This includes the exchange of professional personnel on the Fellowship level. Forty-three bone marrow transplantations on children with acute leukemia have been done at this institution from 11/1/76 to 12/1/79. Collaborative studies continue in immunology with the Fred Hutchinson Cancer Research Center, primarily through the efforts of Irwin D. Bernstein, M.D.

BIBLIOGRAPHIC REFERENCES: Bleyer, W.A., Krivit, W., Chard, R.L., Hammond, D.: Phase II study of VM-26 in acute leukemia, neuroblastoma and other refractory childhood malignancies. Cancer Treat. Rep. Vol. 63 6:977-981, 1979. Nesbit, M., Chard, R., Evans, A., Karon, M., Hammond, G.D.: Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. Am. J. Pediatr. Hematology/Oncology Vol. 1, 1:9-13, 1979.

## B. BROAD CLINICAL PROGRAMS

### 288. PEDIATRIC ONCOLOGY PROGRAM PROJECT

*Krivit, W., Kersey, J. H.,* University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The Pediatric Oncology Program Project is an integrated grant covering clinical and preclinical studies in oncology and bone marrow transplantation. A major emphasis of this grant is related to therapeutic investigations with emphasis on marrow transplantation for the treatment of acute leukemia, non-Hodgkin's lymphoma, neuroblastoma, aplastic anemia, and for patients at high risk for kidney graft rejection. Children and adults will be treated in these studies. Emphasis is on total lymphoid irradiation and T-cell depletion of donor bone marrow to reduce the risk of development of graft versus host disease. Preclinical investigations form a major portion of this grant, complementing and interdigitating with the therapeutic studies. Included are investigations into the nature and function of committed hematopoietic marrow cells, platelet pathophysiology, cyclophosphamide metabolism, and adrenergic mechanisms in neuroblastoma. Studies of the etiology of childhood cancers will include evaluation of the role of DNA repair mechanisms and tumor viruses.

### 289. CHILDREN'S CANCER RESEARCH CENTER

*D'Angio, G. J.,* Children's Hospital of Philadelphia, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania,* 19104, United States of America

The program of the Children's Cancer Research Center focuses on the special problems of pediatric oncology and seeks: 1) To devise better and more efficient treatments using clinical and laboratory studies so as to achieve best survival and lowest early and delayed complication rates. 2) To study and understand the late adversities of therapy so that they can be avoided or mitigated. 3) To identify causative factors with a view towards reducing the incidence of childhood cancer.

Integrated clinical, epidemiologic and laboratory investigations will be used to accomplish these objectives. Leukemia, neuroblastoma and other tumors and disease states of neural crest origin will be emphasized in clinical studies and those relating to the genetics, immunology, membrane biology, epidemiology and radiobiology of pediatric neoplasia. The development of minimal therapies for low risk patients and aggressive treatments, including those requiring bone marrow rescue for children at high risk, will be stressed.

The late effects of treatment will be studied, with special reference to the learning disabilities that follow cranial irradiation for leukemia and other cancers.

### 290. GENERAL CLINICAL RESEARCH CENTER

*Pratt, E. L., Daniels, R. S., Partin, J. C., Hug, G.,* Children's Hospital Medical Center, Dept. of Pediatrics, *3245 Burnet Ave., Cincinnati, Ohio,* 45229, United States of America

This is an application for continued support of a multidisciplinary Clinical Research Center for children at the Children's Hospital, Cincinnati, Ohio. The Center will provide eight beds for use by all departments of the University of Cincinnati Collge of Medicine and members of the Children's Hospital Research Foundation.

### 291. GENERAL CLINICAL RESEARCH CENTER

*Levin, W. C., Poffenbarger, P. L.,* University of Texas, Medical Branch at Galveston, School of Medicine, Dept. of Internal Medicine, *300 University Blvd., Galveston, Texas,* 77550, United States of America

This grant application is requested for continuing support of the existing Clinical Research Center (CRC) at the University of Texas Medical Branch. This CRC is presently (1980) in its 18th grand-funded year. It is a mixed (adult-child) 8 funded bed

unit presently located on the 6th floor of the Child Health Center.

The major clinical research projects presently conducted within the CRC include studies on sleep apnea, hypertension, diabetes mellitus, aplastic anemia, immune deficiency states, lymphocyte depletion in preparation for renal transplantation, gastrointestinal hormone physiology, and malabsorption syndromes in infancy and childhood. Over 40 faculty members from both the Basic and the Clinical Science Disciplines are involved in these investigations.

This federally funded center serves an essential function at UTMB, providing the necessary hospital facility and support personnel to perform such human investigations, and to train future clinical investigators.

**292. GENERAL CLINICAL RESEARCH CENTER**

*Deal, W. B., Rosenbloom, A. L., Cerda, J. J.,* State University System of Florida, University of Florida, School of Medicine, Dept. of Medicine, *1600 Archer Rd., Box J-266, Gainesville, Florida,* 32610, United States of America

This proposal is for continuation of a seven-bed inpatient and outpatient CRC for children and adults at the Shands Teaching Hospital of the J. Hillis Miller Health Center of the University of Florida, to provide careful and optimal control of variables critical to clinical investigation in man. The Center is organized to provide a focus for communication and collaboration among health scientists advising on policy and carrying out studies in the unit, including specialists in: gastroenterology, pediatric and adult endocrinology, obstetrics and gynecology, metabolism, genetics, immunology, microbiology, oncology, pediatric and adult general surgery, urology, hematology, neurology, pathology, ophthalmology, psychiatry, psychology, biochemistry, pharmacology, nursing, pharmacy, pulmonology, and pediatric nephrology. Research-oriented nursing and dietary staff assist in the development of detailed and practicable protocols and assure adherence to them. The Program Director and Associate Director, assisted by the Advisory Committee, encourage and assist young investigators to develop clinical research proposals. A technician is responsible for dependable specimen handling and distribution and carries out assays of urine and blood constituents to assist investigators and save costs.

**293. CLINICAL CANCER RESEARCH PROGRAM**

*Drezner, M., Seigler, H. F., Huang, A. T., Paulson, D., Metzgar, R., Lyles, K., Laszlo, J.,* Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

This program project renewal application seeks support for multidisciplinary clinical research projects dealing with proposals for new methods of diagnosis and treatment of cancer. The leukemia-lymphoma program has projects in autologous bone marrow transplantation, childhood ALL, studies of newly described morphologic particles, research on lymphoproliferative and myeloproliferative disorders, leukemia immunology, platelet antigens, and biochemical pharmacologic studies of new lipid soluble folate antagonists. Additional programs are described in urologic oncology, which include a range of projects from ultrastructure, culture of human cells and clinical chemotherapy through to metabolic studies of new findings of tumor induced osteomalacia, and prognostic factors in prostatic cancer. Interdisciplinary programs in lung cancer, head and neck cancer, breast cancer, malignant melanoma, and brain tumors are also presented in this application.

The central feature of this request is that we have a newly constructed facility in which multidisciplinary research can be conducted and which provides the optimal conditions for education and patient care and enables the collection of research materials for laboratory investigations. The clinical faculty has been greatly expanded and the scope of research increased accordingly.

**294. CANCER CENTER SUPPORT (CORE) GRANT**

*Mauer, A. M., Harrington, R. L., Granoff, A., Simone, J. V., Adler, F., Morrison, M., Welch, A.,* St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

The objectives of this program are to provide for the opportunity of clinical and laboratory research and education involving specifically the problems of childhood cancer and also to provide the opportunity for a broad based study of the fundamental aspects of the biology of cancer. Currently through this program, care is being provided for 1,600 children with cancer. Treatment programs are conducted according to research protocols in order to provide the opportunity for continuous improvement of treatment regimens and also the necessary data acquisition for the development of new knowledge concerning the clinical aspects of childhood cancer. In addition, there are four divisions of laboratory research: virology, biochemistry, pharmacology and immunology. Many opportunities are being realized for coordinative research involving both the clinical and the laboratory investigators. CORE grant support permits the accomplishment of these objectives within the unique capabilities of this institution.

**295. CANCER CENTER SUPPORT GRANT**

*Kaplan, H. S., Bagshaw, M. A., Rosenberg, S. A., Nelsen, T. S., Glader, B. W., Dorfman, R. F.,* Stanford University, School of Medicine, Dept. of Radiology, *300 Pasteur Dr., Stanford, California,* 94305, United States of America

Clinical investigations in adult and pediatric oncology, with emphasis on natural history and mode of spread of various types of neoplasms; improved histopathologic diagnosis and classification; improved radiographic, radioisotopic, surgical, and laboratory methods for the detection and localization of primary tumors and their metastases; improved clinical staging of neoplasms; longitudinal studies, in vivo and in vitro, of immunologic responsiveness in patients with different forms of cancer as a function of stage of disease and of treatment; longitudinal studies of the prognostic significance of various biochemical and immunologic parameters; randomized and nonrandomized clinical therapeutic trials aimed at optimizing therapy for cancers of particular types and stages; studies of the infectious complications of certain types of cancer and of the influence of chemotherapy, radiotherapy, and staging laparotomy with splenectomy on susceptibility to bacterial, viral and fungal infection; quantitative clinical pharmacology of selected cancer chemotherapeutic agents; and preliminary clinical studies of the possible enhancement by hyperthermia of the efficacy of radiotherapy and chemotherapy.

**296. CANCER CENTER SUPPORT GRANT (SPECIALIZED)**

*Camitta, B. M.,* Medical College of Wisconsin, School of Medicine, Dept. of Pediatrics, *561 N. 15th St., Milwaukee, Wisconsin,* 53233, United States of America

The diagnosis of cancer in a child is no longer synonymous with death. However, cancer is still the leading cause of death from disease in American children over one year of age. In addition, most of the major advances in treatment were made prior to 1970 and the dismal prognoses of some tumors (T cell leukemia, disseminated neuroblastoma) remain unchanged. Even in therapy-responsive tumors such as common cell ALL, lymphomas and Wilms' tumor, 20-30% of children relapse. Clearly there is a need for more fundamental knowledge about the origin, biologic properties, subtypes, and reasons for varying responsiveness to therapy of different childhood tumors.

The Midwest Children's Cancer Center is a clinical research facility, associated with research laboratories focusing on problems generated by patient care. The six general objectives of the Center are: (1) Determination of pharmacokinetics, mechanisms of action and efficacy of new anti-cancer drugs; (2) development of further understanding of the immune system in children with cancer and possible ways of utilizing it for treatment; (3) development of new anti-cancer treatments by comparative and exploratory studies; (4) assessment of infectious problems in children with cancer and ways of treating or preventing them; (5) provision of childhood cancer education for physicians, basic scientists, students, nurses, and the public; (6) collaboration with neighboring institutions, other Cancer Centers and community programs.

On a larger scale, the Cancer Center's aim is to generate awareness, interest and involvement in childhood cancer by the medical community and lay public. It also serves as a model for organization of care and research for other life threatening diseases requiring intensive long-term multidisciplinary treatment.

BIBLIOGRAPHIC REFERENCES: Pinkel, D., Hustu, H.O., Aur, R.J.A., Smith, K., Borella, L., and Simone, J.: Radiotherapy in leukemia and lymphoma of children. Cancer, 39:817, 1977. Borella, L., Sen, L., Dow, L.W., and Casper, J.T.: Cell differentiation versus tumor-related antigens in childhood acute lymphoblastic leukemia (ALL). Clinical significance of leukemia markers. Haematology and Blood Transfusion 20:77-85, 1977.

### 297. COMMUNITY CHILDHOOD CANCER CONTROL FOR FLORIDA

*Talbert, J. L.*, Florida Assn. of Pediatric Tumor Programs Inc., J. Hillis Miller Health Center, *Box J 286, Gainesville, Florida,* 32610, United States of America

The primary objective of this application is to demonstrate the feasibility of expanding an existing network of childhood cancer clinics into a comprehensive program which will ensure availability of quality cancer care for every child in the State of Florida. This statewide program will be aimed toward the improvement of early detection, medical treatment and continuing care and rehabilitation of pediatric cancer patients. Proposed methods for the achievement of this goal are improved education of the lay public and community physicians, the adoption of national treatment protocols for all patients, the establishment of new children's cancer treatment centers, the extension of advanced methods of children's cancer management into the local community, and a greater emphasis on the psychosocial aspects of cancer management in children. The Florida Association of Pediatric Tumor Programs, Inc., a unique organization of Florida physicians who are dedicated and knowledgeable in the field of pediatric oncology, will provide the vehicle for coordination and development of this comprehensive statewide attack on childhood cancer.

### 298. COMMUNITY-BASED THERAPY FOR CHILDREN WITH CANCER

*Kisker, C. T.*, University of Iowa, School of Medicine, Dept. of Pediatrics, *Oakdale, Iowa,* 52319, United States of America

The research objective is to study the management of children with cancer by tertiary care center-based pediatric hematologists and private practitioners who are systematically utilizing communication and record-keeping support services. This shared management system of health care delivery is being compared with the standard practice of having all diagnostic and therapeutic measures for these patients provided by hospital-based hematologists.

Examination is being made of the outcome of patients managed by hematologists and private practitioners and of patients managed solely by hematologists. Of particular interest is the incidence of fever, infection, drug toxicity, neutropenia, deviation from chemotherapy treatment plan and the number of hospitalizations in the two groups.

Additional longitudinal studies of school attendance, educational achievement, school and home behavioral problems, intelligence, and emotional stability are being carried out.

The design also includes examination of the time and monetary resources consumed by rural pediatric cancer patients. Cost analyses are being made of the support services required by the shared management system of delivering medical care.

Stability of referral patterns for pediatric cancer patients prior to and during the project (1970-1979) is being investigated.

### 299. CLINICAL TRIALS IN PEDIATRIC PATIENTS

*Higgins, G. R.*, Children's Hospital of Los Angeles, *4650 Sunset Blvd., Los Angeles, California,* 90054, United States of America

OBJECTIVES: Conduct Phase I studies to determine the clinical toxicology and maximal tolerated doses of potentially useful chemotherapeutic agents. Conduct Phase II studies to determine the spectrum of activity of new agents in pediatric malignancies, and conduct clinical pharmacologic studies to characterize the distribution and metabolism of anti-cancer agents in children.

### 300. CLINICAL TRIALS IN PEDIATRIC PATIENTS

*Tan, C. T.*, Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

OBJECTIVES: Conduct Phase I studies to determine the clinical toxicology maximal tolerated doses of potentially useful chemotherapeutic agents. Conduct Phase II studies to determine the spectrum of activity of new agents in pediatric malignancies, and conduct clinical pharmacologic studies to characterize the distribution and metabolism of anti-cancer agents in children.

### 301. STUDIES OF INDICINE-N-OXIDE WITH PEDIATRIC PATIENTS

*Miser, J. S.*, Ohio State University, Columbus Campus, School of Medicine, Dept. of Pediatrics, *370 W. 9th Ave., Columbus, Ohio,* 43212, United States of America

OBJECTIVES: Conduct Phase I studies to determine the clinical toxicology and maximal tolerated doses of potentially useful chemotherapeutic agents. Conduct Phase II studies to determine the spectrum of activity of new agents in pediatric malignancies, and conduct clinical pharmacologic studies to characterize the distribution and metabolism of anti-cancer agents in children.

### 302. CLINICAL TRIALS IN PEDIATRIC PATIENTS

*Sullivan, M.*, University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

OBJECTIVES: Conduct Phase I studies to determine the clinical toxicology and maximal tolerated doses of potentially useful chemotherapeutic agents. Conduct Phase II studies to determine the spectrum of activity of new agents in pediatric malignancies, and conduct clinical pharmacologic studies to characterize the distribution and metabolism of anti-cancer agents in children.

### 303. CLINICAL EVALUATION OF CANCER CHEMOTHERAPY IN CHILDREN

*Tan, C. T.*, Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 304. CIS-DIAMINO PLATINUM EFFECT IN PEDIATRIC NEOPLASMS

*Necheles, T. F.*, Tufts - New England Medical Center Hospital, *171 Harrison Ave., Boston, Massachusetts,* 02111, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 305. HIGH DOSE METHOTREXATE FOR CHILDHOOD MALIGNANCIES

*Wong, K. Y.*, Children's Hospital Medical Center, *3245 Burnet Ave., Cincinnati, Ohio,* 45229, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 306. TRANSFER FACTOR THERAPY IN LEUKEMIA AND IMMUNE DEFICIENCY DISEASES

*Lampkin, B. C.*, Children's Hospital Medical Center, *3245 Burnet Ave., Cincinnati, Ohio,* 45229, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 307. PEDIATRIC ONCOLOGY

*McIntosh, S. L.*, Yale University, School of Medicine, Dept. of Pediatrics, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 308. PEDIATRIC TUMORS (HUMAN)

*Kaizer, H.*, Johns Hopkins University, School of Medicine, Dept. of Pediatrics, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 309. CHILDHOOD NEOPLASMS

*Zinkham, W. N.*, Johns Hopkins University, School of Medicine, Dept. of Pediatrics, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 310. PEDIATRIC NEOPLASMS

*Nathan, D. G.*, Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 311. MANAGEMENT OF PEDIATRIC CANCER

*Burgert, E. O.*, Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 312. NUTRITIONAL STATUS OF CHILDREN WITH CANCER

*Graham Pole, J.*, University Hospitals of Cleveland, *2065 Adelbert Rd., Cleveland, Ohio*, 44106, United States of America

This is part of a broader project. A summary of this subproject is not available.

### 313. PEDIATRIC ONCOLOGY (HUMAN, MICE, MONKEYS)

*Hartmann, J. R.*, Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

## C. EDUCATIONAL PROGRAMS

### 314. CANCER INFORMATION EXCHANGE

*Meadows, A. T., D'Angio, G. J., Kramer, S., Jarrett, P.*, University of Pennsylvania, Children's Hospital of Philadelphia, Dept. of Medicine, *34th St. & Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

Rapid progress is being made in cancer management with consequent better survival rates, and an increased understanding of the adversities of successful treatment. Many of these advances have been made within cancer centers, and the swift transfer of new information therefrom to physicians in the community is highly desirable. Centers in turn rely on the early referral and on follow-up information provided by community physicians in order to continue these advances. This proposal is concerned with the development of programs for the early and full exchange of information between Centers and non-Center-related health professionals so that the latest and best diagnostic therapeutic and follow-up measures can be shared by patients in Centers and in the Community. Children with cancer simplify such program development because the types of cancer are few, and recent treatment successes have been notable and can be attributed to specific therapeutic measures that can be identified. This Center has the Greater Delaware Valley (GDV) Pediatric Tumor Registry as a resource for such a project. The registry is population-based and collects information regarding all children seen at 140 institutions within the GDV.

The proposal is divided between two stages: 1) Planning (one year) and 2) Program Development (three years). Measures found to be effective for pediatric oncology can be applied to adults as well.

### 315. CLINICAL CANCER EDUCATION PROGRAM/ PEDIATRICS

*Leikin, S. L., Champion, L. A., Movassaghi, N., Randolph, J. G.*, Children's Hospital National Medical Center, *111 Michigan Ave. N.W., Washington, District of Columbia*, 20010, United States of America

In order to increase and extend better pediatric cancer care into the community an expansion of the educational program at the Children's Hospital National Medical Center is proposed. The position of cancer education coordinator will be established. This individual's responsibility will be to arrange for teaching seminars in the basic and clinical sciences relative to pediatric cancer. The educational program will be directed at medical students, house staff, and practicing physicians. The teaching associates will assist in this instruction. In turn, the teaching associates will be the recipients of advanced training in pediatric oncology by the full-time staff and outside resources as developed by the cancer education coordinator. The cancer education program will be both intramural and extramural. In conjunction with this effort a series of audio-visual slide programs will be prepared and utilized for educational purposes and will be distributed to a number of health related organizations. In addition, a booklet will be prepared for distribution to parents of patients and to the lay public to instruct them in the basic facts about the more common solid tumors of infancy and childhood.

### 316. CLINICAL CANCER EDUCATION PROGRAM

*Evans, A. E., Raney, R. B., Fergusson, J., Ross, J., Combrinck Graham, L.*, Children's Hospital of Philadelphia, Division of Oncology, *3400 Civic Ctr. Blvd., Philadelphia, Pennsylvania*, 19104, United States of America

The purpose of this Clinical Cancer Education Program is to provide a wide range of clinical cancer education in pediatric oncology to students of different disciplines and many levels of education. The clinical program of the Division of Oncology serves as the educational 'laboratory' for the students who are provided with a core program of rounds and lectures; individual programs are designed for each student's special needs. The students range from undergraduates in the fields of dentistry, medicine, nursing, social service, to advance full-time trainees planning a career in academic pediatric oncology. It is the aim of the program to portray the ideal care of a child with cancer in the hospital, the outpatient clinic and the community, using multimodal therapy and supportive care in a continuum from diagnosis until long after death, should it occur.

### 317. CLINICAL CANCER EDUCATION PROGRAM

*Lampkin, B. C., Wong, K. Y., Maloney, M., Bove, K. E., Hollan, C. S., Gruppo, R. A., Neely, J.*, Children's Hospital Medical Center, Dept. of Pediatrics, *3245 Burnet Ave., Cincinnati, Ohio*, 45229, United States of America

The purpose of our cancer education program is to educate both medical and nonmedical groups regarding childhood cancers with the hope that this will lead to a better understanding of cancer in general and that children with cancer will be better diagnosed, treated and rehabilitated.

We plan to teach the principles of oncology, with emphasis on childhood cancers, to medical students, pediatric house staff, post-pediatric residency trainees in pediatric hematology-oncology and pediatric surgery, practicing physicians, nurses, allied health professionals (pediatric dentists, pharmacists, radiation therapy technologists, physical therapists and occupational therapists, laboratory technicians, public health nurses, hospital dieticians and clergy), parents of children with cancer, the business community and lay public.

Our methods of educating medical personnel will include lectures, conferences, seminars, direct patient experience, and participation in clinical research protocols and projects.

Our education program for the lay public will also include lectures, seminars and conferences but emphasis in this program will be tailored to meet the needs of parents, teachers, and leaders in the business community.

### 318. CLINICAL CANCER EDUCATION PROGRAM

*Hays, D. M.*, Children's Hospital of Los Angeles, *4650 Sunset Blvd., Los Angeles, California*, 90054, United States of America

This proposal is submitted by the staff of a pediatric teaching hospital in the Departments of Pediatrics, Surgery, Pathology, Psychiatry, and The Basic Sciences of the University of Southern California. The staff includes 19 doctors whose major interest is in clinical oncology and/or cancer research. The institution is a cancer center admitting 160 new pediatric patients with neoplasms per year; an active member of a cooperative group, Children's Cancer Study Group; and a participant in all intergroup or national studies of pediatric cancer patients. Nine major basic cancer research projects are in progress.

It is proposed that the resources for education in pediatric oncology noted above be employed in a series of projects directed at medical students, postgraduate physicians in training, physicians in practice, nursing and allied health service personnel. These programs will attempt to disseminate concepts of (a) the importance of early cancer detection; (b) current forms of diagnosis and multidisciplinary management; (c) involvement in related psychosocial problems; (d) rehabilitation in the care of

children with malignancy; and (e) objective evaluation of the results of cancer therapy. This educational effort will be correlated with the Cancer Control Program, activities of the cooperative group and other phases of cancer education in the University and the Cancer Center.

### 319. CLINICAL CANCER EDUCATION PROGRAM/ PEDIATRIC

*Hartmann, J. R., Chard, R. L., Bernstein, I. D., Bleyer, W. A., Johnson, F. L., Pendergrass, T. W., Rudolf, L., Griffin, T. W., Ward, B., Schaller, R., Raskin, J., Beckwith, J. B.,* Children's Orthopedic Hospital & Medical Center, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

The aim of this proposal is to continue to develop a model education program in pediatric oncology for teaching associates, housestaff, practicing physicians, medical students, nurses, social workers and other paramedical disciplines. Established clinical and research programs of this comprehensive cancer center together with a formal teaching curriculum, conferences and self-teaching audiovisual aids will be used. The program will be responsive to changing needs in pediatric oncology with greater emphasis on epidemiology, pharmacology and the need to develop pediatric oncologists with the ability to develop innovative clinical and laboratory research programs. Frequent and in-depth evaluation of the program will be performed.

BIBLIOGRAPHIC REFERENCES: Chard, R.L., Hartmann, J.R., Bernstein, I.D., Bleyer, W.A., and Johnson F.L.: Acute childhood leukemia. Current Therapy: Howard F. Conn (Ed.), W.B. Saunders Co., Philadelphia p. 309, 1978. Hammond, G.D., Bleyer, W.A., Hartmann, J.R., Hays, D.M., and Jenkin, R.D.T.: Perspectives in pediatric oncology. Cancer 41:29-35, 1978.

### 320. CLINICAL CANCER EDUCATION PROGRAM

*Mauer, A. M., Thompson, E., Simone, J. V., Pratt, C., Wilimas, J., Aur, J.,* St. Jude Children's Research Hospital, *332 N. Lauderdale St., P.O. Box 318, Memphis, Tennessee,* 38101, United States of America

St. Jude Children's Research Hospital has cancer education programs at mutiple levels for clinical and basic science students. A 3-month rotation for clinical assistants and a 2-year program for clinical associates are available.

The objectives are to train clinicians with expertise in diagnosis and management who can assume care of cancer patients and who can utilize inpatient care, multiple subspeciality and basic research disciplines. Other programs which interdigitate with those for clinical assistants and associates are also described, as are cancer education programs for nurses and community practitioners.

### 321. CLINICAL CANCER EDUCATION PROGRAM

*Camitta, B. M., Lauer, S., Casper, J., Chusid, M. J., Duck, S., Gill, J., Glicklich, M., Herrman, J., Hodach, A., Holcenberg, J., Jacobs, P., Jelsema, C.,* Milwaukee Children's Hospital, Dept. of Pediatrics, *1700 W. Wisconsin Ave., Box 1997, Milwaukee, Wisconsin,* 53233, United States of America

The purpose of this program is to reduce incidence, morbidity and mortality from childhood cancer through education of physicians, nurses and medical students in the prevention, early diagnosis, evaluation, treatment and follow-up care of children with cancer. For medical students, our methods include lectures during their basic science years and assignment to children with cancer, and lectures, discussions and opportunities for elective rotations in oncology during the clinical years. First, second, and third year pediatric trainees attend weekly multidisciplinary tumor conferences and serve as house officers on the cancer research inpatient unit. Post-residency trainees have the opportunity for formal, structured, 1-2 year clinical cancer training experiences leading to careers as pediatric oncologists in group practices, cancer centers or medical schools. Practicing physicians receive cancer education by participation in the care of patients with cancer whom they refer to this center, by participation in tumor conferences, and by periodic presentations concerning childhood cancer at the weekly hospital Grand Rounds and monthly Mortality Conferences. Nurses receive in-service training in the care of children with cancer and participate in rounds and other formal teaching exercises as well.

# INVESTIGATOR INDEX


Ablin, A.R. 273
Adler, F. 294
Aherne, G.W. 168
Ahmed, Q.A. 72
Alberman, E. 46
Albert, R.E. 42
Albert, S. 87
Albo, V.C. 264
Alderson, M.R. 46
Allen, J.C. 277
Altman, Y.N. 128
Alvarado, C. 256
Alvarez, A.M. 1
Ambrosio, A. 190
Anderson, D.E. 15
Anderson, T. 160
Anderson, V. 268
Andreeff, M. 144
Anglesio, E. 93
Angyal, T. 31
Antia, P.K. 164
Aschenbrenner, C. 87
Askin, F.B. 239, 252
Au, W. 15
Aufses, A.H. 242
Aur, J. 320
Austin, D.F. 57, 87
Axelrod, R.S. 156
Baboo, H.A. 68
Bader, J.L. 16
Bader, J.P. 6, 49
Baehner, R.L. 194, 203, 274
Bagshaw, M.A. 295
Bakkeren, J.A. 126
Banfi, A.D. 48
Barbosa, G. 131, 133
Barone, R. 243
Baskin, F. 114
Baum, E.S. 48, 263
Baumgartner, C. 176, 196, 212
Beck, W. 204, 213
Beck, W.T. 175, 198
Becker, K.L. 130
Beckwith, J.B. 202, 319
Becu, L.N. 78
Bell, M.J. 252
Belt, R. 250
Benetos, S. 147
Bensinger, W. 180
Berdron, W.E. 284
Berg, R.A. 223
Bergamini, R. 252
Bernstein, I.D. 319
Berry, D.H. 251
Bilek, O. 59
Bing, D.H. 137
Birch, J.M. 60, 71, 85, 95
Birdsell, J.M. 105
Bischof, C. 282
Bishop, K. 102
Bithell, J.F. 17, 36
Blackstock, R. 253
Blair, A.E. 33
Blanc, W.A. 284
Bleyer, W.A. 319
Blot, W.J. 33
Bobrowsky, R. 51
Boelaert, R. 20
Boldt, W. 64
Boles, E.T. 286
Bonessana, A.C. 186
Bonessana, C.A. 78
Boutros, S.G. 91
Bove, K.E. 317
Bower, R. 252
Boxer, L.A. 194, 274
Bozek, J. 207
Brandes, M.M. 282
Breslow, N. 202
Brown, S.M. 34, 35
Broxmeyer, H.E. 146
Brubaker, G.R. 76
Bruce, D. 275
Bruckman, J.E. 279
Brunell, P.A. 178
Bruzzi, P.A. 32
Bucher, U. 176, 196, 212
Buckner, D. 180
Burgert, E.O. 179, 279, 311
Burrow, G.N. 129
Butterfield, G. 227, 234
Byfield, J. 243
Cairns, N. 249
Cairns, N.U. 227, 234
Calderon, O. 132
Camacho, A. 187
Camacho, M.A. 187, 193, 199, 205
Camitta, B. 160
Camitta, B.M. 218, 296, 321
Campbell, J.R. 270
Campbell, P. 102
Cangir, A. 261
Capece, W. 190
Carrillo, H.J. 193
Casper, J. 321
Casper, J.T. 154
Castro, E. 132, 134
Catalano, E. 190
Cerda, J.J. 292
Chabner, B. 177, 195, 209
Champion, L.A. 315
Chang, C.H. 284
Chang, J. 272
Chard, R.L. 287, 319
Chatten, J. 275
Chilcote, R.R. 274
Child, M.A. 87
Christine, B.W. 89
Chusid, M.J. 321
Civin, C.I. 247
Clark, J.A. 229
Clatworthy, H.W. 286
Clinton, B. 129
Colangelo, M. 190
Collins, R.D. 276
Comaroff, J. 226
Combrinck Graham, L. 316
Cooper, M.D. 245
Cooper, R. 41
Copeland, D.R. 261
Cornell, C.J. 237
Crist, W.M. 245
Cruse, R. 259
Culbert, S.J. 261
Cupps, R.E. 179
Cuttner, J. 242
Czerwinski, W. 207
D'Angio, G.J. 48, 202, 289, 314
Dahl, T. 167
Damle, S.R. 164
Dammacco, F. 111
Daniel, W. 272
Daniels, R.S. 290
Danoff, B. 191
Davidson, J. 282
de Koning, J. 127, 172
De Lopez, B.H. 83
de Vaan, G.A. 19, 126
Deal, W.B. 292
Dearing, V. 256
Dearth, J.C. 245
Decker, D.G. 25
Deisseroth, A.B. 177, 195, 209
Delgado, A. 1
DeLong, E.R. 3
deLorimier, A. 273
Dendaki Svolaki, C. 63, 147
Deodhar, S.D. 239
Derom, R.M. 20
DeSousa, M. 146
Diaz, F. 131
Dick, F. 282
Dickerman, J.D. 237
Distelhorst, C. 286
Doering, E.J. 259
Doerken, H. 69
Domini, R. 200
Donnelly, W. 255
Donoso, J. 125
Dooren, L.J. 172
Dorfman, R.F. 295
Dosch, H. 149
Dougan, L.E. 62
Draper, G.J. 12, 30, 36, 45, 97, 103
Drexner, M. 293
Drucker, W.D. 218
Duck, S. 321
Duck, S.C. 218
Dukkers van Emden, D. 27
Dunger, D.B. 201
Dunn, N.L. 124, 248
Dyment, P.G. 99, 259
Ekert, H. 135, 152, 163, 166, 173, 174, 189, 192
Elahi, M.F. 72
Ellis, R.B. 123, 143
Emmens, R. 268
Erdos, Z. 82
Erenberg, G. 259
Ertel, I. 283
Ettinger, L.J. 268
Evans, A.E. 48, 202, 275, 316
Evans, A.S. 79
Evans, R.G. 279
Evans, W. 204, 213
Evans, W.E. 175, 198
Everson, R.B. 34

Fabian, C. 250
Falcier, F.W. 22
Falletta, J. 182
Falletta, J.M. 101, 254
Favara, B. 272
Feig, S.A. 271
Fergusson, J. 316
Fernbach, D.J. 100, 260
Ferrell, R. 13
Ferrell, R.E. 11
Fife, B.L. 231
Filston, H.C. 254
Finegold, M. 260
Finklestein, J.Z. 278
Fischer, T. 285
Fishburn, R.I. 254
Flannery, J.R. 22
Ford, J.M. 102
Forero, E. 10, 206
Forman, E.N. 237
Fossati Bellani, F. 200
Fox, M. 282
Frankel, L.S. 261
Fraumeni, J.F. 6, 33, 49
Freeman, A.I. 169, 258
Frey, 69
Garbrecht, 69
Garcia, I. 187, 193, 199
Garcia Valles, M.C. 1
Gardner, M.B. 90
Gawadia, M.I. 94
Gaynon, P. 263
Gelfand, E.W. 149
Genel, M. 129
Gentle, T. 142
George, S. 204, 213
George, S.I. 4, 113, 175, 198
Gertner, J.M. 129
Geser, A. 75, 76
Ghavimi, F. 208
Giardina, E.D. 111
Gidwani, G. 259
Gilchrist, G.S. 179, 279
Gill, J. 321
Gilles, F.H. 155
Gilman, P.A. 16
Glader, B.W. 295
Glatstein, E. 177, 195, 209
Glaubiger, D. 177, 195, 209
Glicklich, M. 321
Glicksman, A.S. 244
Goellner, J.R. 279
Goh, K. 41
Gold, E. 65
Gomez, J. 10, 206
Gomez, M.R. 89
Gordis, L. 65
Graham Pole, J. 312
Graham Pole, J.R. 201
Granoff, A. 294
Grasedyck, 69
Grebe, G. 125
Green, A. 204, 213
Green, D. 48
Greipp, P.R. 179
Gresik, V.M. 260
Griffin, P.P. 276
Griffin, T.W. 319
Groom, G.L. 231
Grose, C.E. 178
Grosfeld, J.L. 194, 203, 274
Gross, S. 99, 266
Grufferman, S. 3, 81, 101
Gruppo, R. 285
Gruppo, R.A. 317
Guansing, A.R. 218
Guenther, 69
Guerrero, L.J. 205
Gutensohn, N. 79
Gutierrez, R. 10, 206
Haanen, C.A. 19
Haegerstrand, I. 18
Haff, A.C. 156
Hagen, T.C. 218
Hahn, J.F. 259
Hahn, T. 139, 157
Hahn, T.C. 128
Haidas, S. 63, 147
Hale, S. 256
Haller, A.J. 247
Hamilton, P.M. 43
Hammond, G.D. 281
Hanash, S. 283
Hanawa, Y. 104
Handzel, Z.T. 128
Hanson, M. 16
Hanson, M.R. 2
Hanson, T. 283
Harnden, D.G. 45
Harrington, R.L. 294
Harris, R. 285
Harrison, M. 273
Harrison, M.W. 270
Hartman, G. 232
Hartmann, J.R. 313, 319
Hassinger, D. 2, 16, 52
Hathaway, W.E. 183
Hauck, R.J. 235
Hauge, M. 18
Hawkins, E.P. 260
Hawkins, H. 256
Hayes, A. 175, 198, 204, 213
Hays, D.M. 318
Hazra, T.A. 248
Heasman, M.A. 45
Heidelberger, K. 283
Heideman, R. 272
Heller, R.M. 276
Hemminki, K.J. 106
Hempelmann, L.H. 41
Henderson, B.E. 90
Herrman, J. 321
Hersh, S.P. 228
Herson, J. 14
Heyn, R.M. 283
Hickman, B.T. 257
Higgins, G.R. 280, 299
Hiilesmaa, V.K. 28
Hill, B.T. 116, 121
Hillier, V. 71
Hirayama, T. 92
Hoagland, H.C. 179
Hobbs, N. 235
Hodach, A. 154, 321
Hoediasmoro, D.S. 73, 74
Hoel, D.G. 35
Holcenberg, J. 321
Holcenberg, J.S. 160
Hollan, C.S. 317
Holland, J.F. 242
Holland, R. 283
Holmes, F.F. 53
Holroyde, C.P. 156
Honig, G.R. 263
Hoogstraten, B. 250
Hoots, W.K. 261
Hoover, R.N. 33
Hope, D. 2
Hopewell, J.W. 117
Hopson, R. 98
Hossain, M.A. 72
Houghton, D.C. 270
Houghton, P.J. 120
Hsu, T.C. 15
Huang, A.T. 293
Hubbard, V.S. 222
Hug, G. 290
Humphrey, G.B. 253
Hustu, H.O. 204, 213
Hutchinson, R.J. 283
Idar, D.A. 128
Imbach, P. 176, 196, 212
Ireys, H.T. 235
Islam, K.M. 72
Iyer, R.V. 257
Jackson, J.F. 257
Jacobs, P. 321
Jaffe, N. 261
Jarrett, P. 314
Jaubert, F. 151
Jelsema, C. 321
Jenkin, R.D. 48
Jensen, N.K. 18
Jimenez, B.R. 187, 193, 199
Jimenez, E. 187, 193, 199
Jimenez, M. 133
Johansen, O.J. 61
Johnson, F.L. 287, 319
Johnson, W.W. 257
Joncas, J.H. 108
Jones, P.H. 95
Jose, D.G. 163
Kabir, M.A. 72
Kaizer, H. 141, 247, 308
Kamphuis, R.P. 172
Kaplan, E. 65
Kaplan, H.S. 295
Kaplan, J. 150
Karbal, A. 117
Kasselberg, A.G. 276
Kastelic, J. 99
Katz, L. 161
Kaufman, R.H. 23
Kay, R. 259
Kay, S. 248
Kelalis, P.P. 279
Keller, R. 154
Kellerman, J. 225
Kersey, J.H. 288
Kessler, I.I. 70
Key, C.R. 87
Khaleque, S.A. 72
Kien, C.L. 160
Kilama, W. 76
Kildeberg, P. 18
Kim, T.H. 256
Kimm, Y.S. 101
King, D. 286
Kinney, T.R. 254
Kinnier Wilson, L.M. 17, 30, 97, 103
Kisker, C.T. 282, 298
Kissane, J.M. 239
Klausz, E. 134
Klemperer, M.R. 268
Klitgaard, H. 218
Klopovich, P. 234
Kneale, G.W. 97
Knudson, A.G. 98
Koch, P. 275
Kolonel, L.N. 87
Koppe, J.G. 27
Korhaz, J. 40
Kramer, S. 98, 314
Kriss, S. 109
Kristoffersen, K. 18
Krivit, W. 288
Kubikova, A.J. 59
Kudrjavcev, T. 89
Kumar, M. 204, 213
Kung, F.H. 184, 232, 243
Kupferschmidt, H.G. 76
Kupst, M.J. 230
Kurata, Y. 138

Kuse, 69
Kushner, J.H. 273
Kyle, R.A. 179
Lahde, P. 217
Lahey, M.E. 265
Lampkin, B. 99
Lampkin, B.C. 285, 306, 317
Land, V.J. 252
Landau, E.Z. 37
Landsberg, L. 129
Lange, B.J. 219
Lansky, S. 249
Lansky, S.B. 227
Lanuza, I. 1
Lapatsanis, P. 147
Laskiewicz, B. 121
Laszlo, J. 293
Latourette, H.B. 56
Lauer, S. 321
Lauer, S.J. 154
Lawrence, W. 238, 248
Lay, H. 102
Leahy, M.A. 162
Leikin, S.L. 267, 315
Lennox, E.L. 103
Leventhal, B.G. 247
Levin, S. 128, 139, 157
Levin, W.C. 291
Levine, A.S. 177, 195, 209, 228
Leviton, A. 87
Li, F.P. 2, 5, 6, 49
Licenziati, F. 190
Lin, R.S. 70
Linder, M.I. 282
Linsell, C.A. 84
Lobel, J. 285
Lobo, J.F. 187, 193, 199, 205
Long, J. 79
Lui, V.K. 256
Luis, D.R. 140
Lukens, J.N. 276
Lundin, J. 37
Lunenfeld, B. 21
Lyles, K. 293
Lyon, J.L. 87
Mack, T.M. 90
MacMahon, B. 79
Magrath, I.T. 177, 195, 209
Maguire, G.P. 226
Mahoney, D.H. 224, 260
Majle, T. 37
Maloney, M. 317
Malpas, J.S. 201, 229
Marcus, R. 255
Marks, K. 259
Marks, V. 168
Marsden, H.B. 45, 60, 71, 85, 95
Martin, F. 132, 133
Martinez, L.C. 206
Martinez Caro, A. 1
Mason, T.J. 33
Matchett, N. 194
Matthay, K. 273
Matthews, J. 163
Matthews, M.L. 62
Matthews, R.N. 163
Mauer, A.M. 204, 213, 294, 320
Maurer, H.M. 238, 248
Maurer, H.S. 263
Mays, C.W. 40
McAdoo, W.G. 231
McIntosh, S.L. 307
McKeen, E.A. 2, 16
McShan, D. 244
McWhirter, W. 102
McWilliams, N.B. 248
Meadows, A.T. 48, 50, 98, 314
Mehta, P. 255
Meigs, J.W. 22, 55
Mellinger, J.F. 89
Menczer, J. 21
Mendelson, J. 243
Mentzer, W. 273
Mertowidjoyo, K.M. 74
Metzgar, R. 254, 293
Meyer, R. 285
Meyers, P.A. 146
Meyn, S. 2
Miah, M.N. 72
Miller, D.R. 277
Miller, R.C. 257
Miller, R.W. 6, 49
Million, R. 255
Minoda, K. 80
Mirkin, D.L. 274
Miser, A. 286
Miser, J. 286
Miser, J.S. 301
Modan, B. 21, 38
Moe, P.J. 47, 61, 167
Mohanakumar, T. 124, 248
Momparler, R.L. 170
Mora, L. 193
Morantz, R. 249
Morgan, E.R. 263
Morgan, K. 105
Morgan, S.K. 240
Morley, A.A. 8
Moroney, R.M. 235
Morris Jones, P. 226
Morris Jones, P.H. 48
Morrison, M. 294
Moss, H.A. 222
Mott, M.G. 142
Movassaghi, N. 267, 315
Mukhopadhyay, N. 260
Muller, H. 122
Mulne, L. 286
Mulvihill, J.J. 2, 6, 16, 49
Munoz, N. 29
Murphy, M.L. 145
Myers, M.H. 52
Nadkarni, J.S. 164
Nadkarni, K.S. 164
Nakajima, F. 204, 213
Nasca, P.C. 88
Nathan, D.G. 67, 310
Navarrete, M. 193
Navarro Gonzalez, J. 1
Necheles, T.F. 304
Neely, J. 285, 317
Neerhout, R.C. 270
Neff, J. 249
Nelsen, T.S. 295
Nesbit, M.E. 239, 269
Neumeister, K. 39
Neutel, I.C. 86
Newman, N. 102
Newton, W.A. 48, 99, 286
Nezelof, C. 151
Nicholls, J. 121
Nicklas, J.W. 263
Nilsonne, U. 214
Nishiya, N. 146
Nitschke, R. 253
Nitzkin, J.L. 41
Nix, W.L. 260
Noell, K.T. 254
Norris, D. 275
Nygaard, R. 47, 167
Nyhan, W.L. 243
O'Brien, M.S. 256
O'Gorman Hughes, D. 102
O'Neill, J.A. 276
Obringer, A. 98
Ochs, J. 220
Odom, L. 272
Odoroff, C. 41
Oei, T.O. 194
Oelsner, G. 21
Okada, S. 138
Oliss, E.G. 77
Olwitt, G. 75
Oorthuys, A.M. 19
Or, A.S. 128
Ordonez, M.P. 1
Ordyniec, J. 207
Ostrowski, I. 140
Pabon, H. 70
Pacsa, A.S. 31
Page, S. 129
Palmieri, A. 190
Panizza, A. 32
Papendieck, C.M. 140
Park, C. 250
Parker, J.E. 64
Parry, D.M. 2, 16
Partanen, T.J. 106
Partin, J.C. 290
Pasca, A. 29
Pastore, G. 93
Patel, N.L. 68
Patel, O.D. 94
Pathak, S. 15
Paulson, D. 293
Pavlovsky, S. 165, 186
Peckham, M.J. 46
Pejtsik, B.A. 31
Pendergrass, T.W. 66, 287, 319
Perek, D. 207
Perez, C.A. 252
Perrin, J.M. 235
Peters, G. 27
Piall, E. 168
Pickle, L.W. 33
Pilch, Y.H. 243
Pineda, G. 1
Piomelli, S. 284
Piza, E.J. 199, 205
Pizzo, P.A. 177, 195, 209, 228
Pless, I.B. 235
Poffenbarger, P.L. 291
Pollice, L.M. 111
Poplack, D.G. 177, 195, 209, 222
Powell, J. 96
Pratt, C. 320
Pratt, C.B. 4, 175, 198, 204, 213, 216
Pratt, E.L. 290
Preston Martin, S. 90
Price, R. 259
Pritchard, J. 116, 121
Provisor, A.J. 194, 274
Pullen, D.J. 257
Puntoni, R. 32
Putnam, T.C. 268
Quddus, F.F. 247
Rabinowitz, R. 268
Raffensperger, J.G. 263
Ragab, A.H. 238, 256
Rahim, M.A. 72
Ramirez, I. 261
Ramsbottom, R.I. 33
Randolph, J.G. 267, 315
Raney, R.B. 238, 275, 316
Raskin, J. 319
Reaman, G. 267
Reardon, M. 2
Reichard, G.A. 156
Rein, G. 116
Reinstein, L.E. 244
Resta, L. 111
Ricardi, V.M. 11
Riccardi, V.M. 13, 260

Rice, M. 102
Rice, M.S. 162
Rickard, K.A. 194, 203
Ried, H.L. 261
Rivard, G.E. 170
Rivera, G. 197, 204, 213
Robboy, S.J. 24
Roberts, F.B. 235
Robinson, M. 99
Robison, L. 239
Rodgers, B. 255
Rodriguez, A. 134
Rodriguez, C. 10, 206
Rodriguez, H. 10, 206
Rogan, W. 34
Rohrbaugh, T. 275
Roloff, J.S. 276
Roion, P.A. 83
Romhanyi, E. 82
Ron, E. 21
Roper, M. 245
Rosen, G. 210, 211
Rosenau, W. 273
Rosenberg, R.N. 114, 115
Rosenberg, S.A. 177, 195, 209, 295
Rosenblatt, D. 118
Rosenbloom, A.L. 292
Ross, J. 316
Rothbarth, P. 172
Rothermel, K. 286
Rothner, A.D. 259
Rousseaumerck, M.F. 151
Routh, A. 257
Rubin, P. 268
Rudolf, I. 319
Rumke, H. 172
Rupniak, H.T. 116, 121
Russell, E.C. 248
Ruymann, F. 238
Sackmann Muriel, F. 165
Sadoff, L. 51
Sahler, O.J. 268
Salonen, T. 106
Salzberg, A. 248
Sanders, B.M. 12
Sandler, D.P. 34, 35
Santi, L. 32
Santoso Nugrahi, B. 74
Santulli, T.V. 284
Sarma, S.K. 72
Sayar, Y. 109
Schaller, R. 319
Schnitzer, B. 283
Schoenberg, B.S. 89
Schoenberg, D.G. 89
Schretlen, E.D. 126
Schulman, J.L. 230
Schwartz, D.B. 232
Schwartz, L.I. 78
Sedlis, M. 252
Seeger, R. 153
Segel, G.B. 268
Seigler, H.F. 293
Seshadri, R. 7
Seshadri, R.S. 8
Sexauer, C.L. 253
Shah, A.K. 68, 94
Shah, P.M. 68, 94
Shahidi, N.T. 262
Shaw, H.J. 121
Shayne, M.W. 235
Shedd, D. 44
Shepherd, D.A. 100
Shetty, P.A. 164
Shimaoka, K. 44
Shore, R. 41
Sica, M.I. 78
Siegel, S. 48
Silva, O.L. 130
Simmons, G. 256
Simon, R. 177, 195, 209
Simone, J.V. 171, 204, 213, 220, 294, 320
Sinks, L.F. 246
Sitarz, A.L. 284
Skutches, C.L. 156
Smiley, S. 270
Smith, E.I. 253
Smith, P.J. 135, 152, 166, 189
Smith, S. 249
Smith, S.D. 119
Smithson, W.A. 179
Snead, R.W. 248
Soule, E.H. 179
Spaulding, S. 44
Speiser, B.L. 274
Spiess, H. 40
Spinetta, J.J. 232
Spirtas, R. 107
Spjut, H.J. 260
Stalder, G. 122
Starling, K.A. 100, 260
Stelger, E. 259
Steinherz, P.G. 277
Steinitz, R. 161
Stematsky, G.T. 109
Stenback, W.A. 260
Stephens, R. 250
Stephenson, B.L. 33
Steuber, C.P. 100, 181, 260
Stevens, K.R. 270
Stewart, A.M. 30, 97
Stewart, D. 249
Stewart, P. 180
Stolzenbach, 69
Stout, R.A. 99
Strander, H. 214
Stranfjord, S. 255
Stratton, L.B. 239
Strayer, F.H. 282
Strong, L.C. 9, 11, 13, 14, 15, 54, 261
Strope, B.E. 228
Stroup, S.L. 276
Subandiri, S. 74
Suenram, D. 234
Sullivan, M. 302
Sullivan, M.P. 261
Sumaya, C.V. 178
Susman, E.J. 228
Sutherland, G. 7
Sutow, W.W. 238, 261
Swanson, G.M. 79
Swindell, R. 60, 85
Szklo, M. 65
Taboada, H. 125
Talbert, J.L. 255, 297
Tamura, K. 44
Tan, C. 277
Tan, C.T. 188, 300, 303
Tannous, R. 282
Tauro, G.P. 163
Taylor, S. 250
Taylor, T.J. 253
Tefft, M. 202, 244
Templeton, J. 275
Ternberg, J.L. 252
Terracini, B. 93
Tewfik, H. 282
Thar, T.L. 255
Thiery, M. 20
Thomas, E.D. 180
Thomas, P. 252
Thompson, E. 320
Toledano, S. 275
Tonascia, J.A. 65
Toogood, I. 166
Toogood, I.R. 162, 173
Townsend, D.E. 26
Trainin, N. 128
Traka, A. 59
Trueworthy, R. 234, 249
Truman, J.T. 237
Tubergen, D.G. 272
Tunell, W.P. 253
Turtz, M. 215
Tzortzatou, F. 63
Utley, J. 243
Van Eys, J. 261
van Weel Sipman, M.H. 127
Van Zanen, G.E. 58
van't Veer Korthof, E. 127
VanWezel, G. 254
Vargas, G. 193
Vats, T.S. 249
Vercelli, M. 32
Vesikari, T. 217
Vietti, T.J. 185, 241, 252
Vlietinck, R. 20
Vora, S. 284
Vossen, J.M. 172
Voute, P.A. 48
Vrba, M.O. 59
Wagner, H.P. 148, 176, 196, 212
Wagner, V.M. 274
Wald, N.J. 29, 110
Walker, D.R. 255
Wallace, H.J. 233
Wang, H.H. 3, 81, 101
Wara, W. 273
Ward, B. 319
Waskerwitz, M. 283
Wasserman, L.R. 242
Waterhouse, J.A. 30, 96
Waters, K. 135, 152, 189
Waters, K.D. 163, 173, 174, 192
Weetman, R.M. 194, 274
Wehinger, H. 159, 236
Weiner, M. 284
Weiss, N.S. 87
Welch, A. 294
Wells, R.J. 221
Wharam, M.D. 247
Whitaker, J.N. 220
Whitehead, T. 256
Whitehead, V.M. 118
Wilcox, A.J. 34
Wilimas, J. 320
Wilkinson, G.S. 112
Williams, A.O. 77
Williams, E.H. 75
Williams, G. 121
Willis, R. 2
Wolf, B. 124
Wolff, J.A. 284
Wolff, L.J. 270
Wong, K.Y. 285, 305, 317
Wood, B. 268
Wood, G. 249
Woodard, E.D. 41
Woodard, J.R. 256
Yu, A.L. 158, 243
Yuwarini, E.D. 74
Zaizov, R. 109
Zannos Marioles, L. 63, 147
Zarkowsky, H.S. 252
Zeinen, M. 6, 49
Zelter, P.M. 136
Ziegler, J.L. 177, 195, 209
Zinkham, W. 247
Zinkham, W.N. 309
Zinkind, R.A. 112
Zoger, S. 273

# CURRENT CANCER RESEARCH PROJECT REGISTRATION FORM

Send to: **ICRDB PROGRAM**
**National Cancer Institute**
**5333 Westbard Avenue**
**Westwood Building, Room 10A18**
**Bethesda, Maryland 20205**

| ICRDB NUMBER |
| --- |
| DO NOT WRITE HERE |

**PLEASE READ SPECIAL INSTRUCTIONS ON OTHER SIDE**

*If you have already submitted a description of your research to the Smithsonian Science Information Exchange (SSIE), to the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or to the Current Cancer Research Project Analysis Center (CCRESPAC) within the past eight (8) months, please do not fill out this form.*

PLEASE TYPE OR PRINT IN ENGLISH

**1) FULL TITLE OF CURRENT CANCER RESEARCH PROJECT**

**2a) UNIQUE PROJECT IDENTIFICATION NUMBER(S)**

**2b) PROTOCOL NUMBER(S)** (if applicable)

**3) NAME OF ORGANIZATION WHERE RESEARCH IS PERFORMED**

**DEPT./LAB./UNIT:**

**MAILING ADDRESS** (see item F on reverse side):

**COUNTRY:**

**4) INVESTIGATORS** (use 2 initials & last name)

**PRINCIPAL:**

**CO-INVESTIGATORS:**

**5) NAME OF FUNDING ORGANIZATION(S)** (list principal source first)

**6) GIVE MONTH AND YEAR FOR END OF CURRENT FUNDING**

**7) DESCRIBE PROJECT UNDER THREE HEADINGS: 1) OBJECTIVE; 2) APPROACH; AND 3) PROGRESS [optional]** (use specific, technical terms)

**PLEASE CHECK ONE:** _____ **1. This is a description of a NEW Project.**
_____ **2. This is a REVISED description of Project No.**_____
(Insert identification number)

FORM APPROVED: OMB NO. 068-R1441 EXP. AUG. 1983

# CANCER RESEARCH REGISTRY

## A Service of the National Cancer Institute

### INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM

You are invited to complete a Current Cancer Research Project Registration Form PROVIDED you have NOT completed a similar form for the Smithsonian Science Information Exchange (SSIE), the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or for the Current Cancer Research Project Analysis Center (CCRESPAC) during the last eight months.

Your project description will be entered into the National Cancer Institute's (NCI) data base, CANCERPROJ (**Cancer Proj**ects). Your project description will also appear in one or more of the ICRDB publications known as SPECIAL LISTINGs of Current Cancer Research. Every year the ICRDB publishes fifty SPECIAL LISTINGs, each containing project descriptions in different specific oncology research areas. A free copy of a SPECIAL LISTING is automatically sent to each investigator whose project description appears in that SPECIAL LISTING. Thus, investigators are annually made aware of research being carried out in their areas of interest.

## GUIDELINES FOR FILLING OUT THE REGISTRY FORM

A. The description should be submitted by or through the individual who is the **principal investigator** of the project described. Major co-investigators should also be listed.

B. If you are working on more than one project, or if your one project consists of several distinct major segments, please prepare a separate summary form for each.

C. Only **CANCER** research projects which are CURRENTLY **ACTIVE** and CURRENTLY **FUNDED** should be submitted.

D. If you are submitting a clinical protocol, please send a copy of the complete protocol. The NCI has an established format which will be used to develop a standard protocol summary. A copy of the prepared summary will be sent to you for review prior to its entry into the data base.

E. Return to address shown on the front of this form.

F. IMPORTANT. If you prefer to have your copy of the SPECIAL LISTING mailed to your home address, or if your co-investigators have different mailing addresses, please list each name and address on a separate sheet of paper.

*U.S. GOVERNMENT PRINTING OFFICE : 1981 O-341-807/128

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
5285 Port Royal Road
Springfield, Va. 22161

OFFICIAL BUSINESS
Penalty for Private Use, $300
PRINTED MATTER

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF COMMERCE
COM-211

THIRD CLASS
BULK RATE

SL-439

**NOTICE OF MAILING CHANGE**

☐ Check here if you wish to discontinue receiving this publication.

☐ Check here if your address has changed and you wish to continue receiving this publication. (Be sure to furnish your complete address including zip code.)

Tear off cover with address label still affixed and send to:

Computer Support Center
ICRDB Program
IIT Research Institute
10 West 35th Street
Chicago IL. 60616